CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 125249/0

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 21, 2008
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
Thru:	Denise P. Toyer, PharmD, Deputy Director D.P. Toyer 2/26/08
	Carol A. Holquist, RPh, Director D.P. Toyer for Carol Holquist 2/26/08 Division of Medication Errors and Technical Support (HFD-420)
From:	Linda Y. Kim-Jung, PharmD, Team Leader LKJ 2/28 Division of Medication Errors and Technical Support (HFD-420)
Subject:	DMETS Label and Labeling Review
Drug Name(s):	Arcalyst (Rilonacept) Lyophilized Powder for Injection 220 mg vial
Application Type/Number:	BLA 125249
Applicant:	Regeneron Pharmaceuticals, Inc
OSE RCM #:	2008-268

CONTENTS

EXECUTIVE SUMMARY

Our analysis of the revised container labels, carton and insert labeling for Arcalyst noted several areas of concern with respect to the presentation of information on the labels/labeling. Addtionally, we have noted areas of vulnerabiltiy with the sponsor's proposal for patient's acquistion of the product and ancillary supplies and the proposed ——— These concerns need to be addressed prior to approval in order to minimize the potential for medication errors and improve the readability and comprehension of the information. Specific recommendations to address these safety concerns are listed in Section 5.

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a February 8, 2008 request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170) for a review of the revised container label, carton labeling, and Arcalyst education materials.

1.2 REGULATORY HISTORY

DMETS notes that the tradename, Arcalyst, was previously reviewed (OSE Review 2007-1559 dated November 16, 2007) and we had no objections to the use of the proposed proprietary name. The revised labels and labeling evaluated in this review were submitted in response to DMETS recommendations from our previous review.

1.3 PRODUCT INFORMATION

Arcalyst is a lyophilized product containing 220 mg of Interleukin-1 (IL-1) Trap in a sterile, single-use vial. The expected duration of therapy was not described, but Arcalyst is being developed for — treatment of CIAS1-associated periodic syndromes, which are designated CAPS. CAPS are a collection of hereditary periodic fever syndromes associated with mutations in the CIAS1 gene, and include Neonatal Onset Multisystem Inflammatory Disorder (NOMID), Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS). The proposed dose of Arcalyst is 160 mg (2 mL) injected subcutaneously once weekly. The lyophilized powder will be reconstituted with 2.3 mL sterile water for injection. After reconstitution, the solution will have a concentration of 80 mg/mL. Each vial contains 220 mg of Arcalyst. Arcalyst will be stored at 2-8°C (36 -46°F) prior to administration. The reconstituted solution may be kept at room temperature but should be used within three hours of reconstitution. Arcalyst does not contain preservatives and unused portions should be discarded after a single withdrawal of drug.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. DMETS defines a medication error as any preventable event that may cause or

lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling have in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMETS staff analyzes reported misuse of drugs, DMETS staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

For this product, the applicant submitted container labels and carton labeling on February 20, 2008 and proposed "Patient Acquisition of Product and Ancillary Supplies" and a [redacted] on February 8, 2008. See Appendices for images of the labels and labeling submitted.

3 RESULTS

3.1 CONTAINER LABELS AND CARTON LABELING

The graphic on the left side of the principal display panel is more prominent than other important information such as the established name, product strength, and storage information.

3.2 SPONSOR'S PROPOSED "PATIENT ACQUISITION OF PRODUCT AND ANCILLARY SUPPLIES"

DMETS does not believe that the initial one time hands-on training at the physician's office is adequate enough to provide assurance that the patient or the caregiver will be able to properly prepare and administer the product.

The proposed plan does not provide assurance that the patient will take the drug vials back to the physician's office for the initial one time hands-on training. It is also possible that the patient may [redacted] and attempt to prepare and administer the product without proper training by their healthcare provider.

The functionality for the specialty pharmacy appears to be more of monitoring patient compliance and re-ordering the drug/supplies rather than for qualitative assessment of patient's knowledge on how to properly prepare and administer the product.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.3

Please refer to OSE #2007-2486 (dated February 21, 2008) by the Patient Labeling and Education Team of the Division of Risk Management (DRISK) for specific recommendations regarding patient's comprehensibility of the Patient Package Insert and Patient Instructions for Use, as some of their comments pertains to the proposed patient educational materials. Additionally, as per agreement with DDMAC, please consult DDMAC for their advisory comments on the

DMETS believes that ideally, all the information pertaining to the disease and treatment along with the drugs/supplies should go directly to the physician's office so that the physician can go over the information in detail with the patient/caregiver in person. Given the complexity of the product preparation and administration, creating such interaction between the physician and the patient is necessary to allow for a clearer understanding of the disease state and treatment.

4 DISCUSSION

The Label and Labeling Risk Assessment findings indicate that the presentation of information and layout design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors with Arcalyst.

4.1 CONTAINER LABELS AND CARTON LABELING

DMETS acknowledges that the presentation of the graphic on the principal display panel is improved from the previous submission; however, the graphic is still very prominent and detracts attention away from important information such as the product strength and storage information.

4.2 SPONSOR'S PROPOSED "PATIENT ACQUISITION OF PRODUCT AND ANCILLARY SUPPLIES"

DMETS does not believe that the initial one time hands-on training at the physician's office is adequate to ensure patients or the caregivers will be able to prepare and administer the product correctly. Additionally, the proposed plan does not provide assurance that the patients will return to the physician's office for the initial one time hands-on training.

. Also, as stated in our previous review, DMETS is concerned that the patient may draw up more than the intended amount (i.e., 2 mL or 160 mg) due to fact that the vial would actually contain 220 mg of riloacept after reconstitution with 2.3 mL of sterile water for injection (SWFI). Likewise, DMETS also questions the size of the SWFI vial to be supplied to the patient. If it is a larger amount (i.e., 5 mL) than the proposed 2.3 ml, then there is also the potential that the patient can withdraw a larger amount of diluent for reconstitution resulting in wrong dose.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and layout design of the proposed container label and carton labeling introduces vulnerability to confusion that could lead to medication errors with Arcalyst. Additionally, we have identified areas of vulnerability in regard to the sponsor's proposal for patient acquisition of product and ancillary supplies along with their proposed [redacted] DMETS believes the risks we have identified can be addressed and mitigated prior to approval, and provide recommendations in Section 5.1, below, that aim at reducing the risk of medication errors.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the applicant pertaining to this issue. If you have further questions or need clarification, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

5.1 CONTAINER LABELS AND CARTON LABELING

5.1.1 Minimize or delete the graphic on the left side of the principal display panel.

5.2 SPONSOR'S PROPOSED "PATIENT ACQUISITION OF PRODUCT AND ANCILLARY SUPPLIES"

5.2.1 We do not believe the sponsor's proposed plan would adequately train the patient/caregiver for proper preparation and administration of the product. Additionally, the proposal fails to monitor the patient's qualitative assessment of the proper use of the drug product.

5.3 [redacted]

5.3.1 All the information pertaining to the disease and treatment along with the drugs/supplies should go directly to the physician's office where the physician can go over the information in detail with the patient/caregiver in person. The patient then can be given the written instructions only after proper training and counseling at the physician's office.

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 22, 2008
To:	Bob A. Rappaport, M.D., Director Division of Anesthesia, Analgesia and Rheumatology
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)
Drug Name(s):	Arcalyst (rilonacept) Injection for subcutaneous use
Application Type/Number:	BLA# 125249/0
Applicant/sponsor:	Regeneron Pharmaceuticals, Inc.
OSE RCM #:	2007-2486

1 INTRODUCTION

Regeneron has been granted Orphan designation by the FDA for IL-1 TRAP (rilonacept) for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS). The sponsor was granted Fast Track designation on May 3, 2006. Based on agreement with the FDA, the sponsor submitted the first submission for a rolling review of an original Biologics Licensing Application, BLA# STN125249 on January 31, 2007, for Rilonacept for the treatment of CAPS.

The sponsor submitted draft labeling for Arcalyst (rilonacept) to the CBER EDR, including a Professional Insert (PI) and Patient Package Insert, sequence number 0003 (original application), on May 25, 2007, version number 1.14.1.3.

The Patient Labeling and Education Team in the Division of Risk Management (DRISK) was requested to review the PPI for Acalyst (riloncept).

2 MATERIAL REVIEWED

- Review Division revised electronic version of the Arcalyst Professional Information (PI) dated February 14, 2008, which was sent to the sponsor on that date.
- Further sponsor revisions received by DRISK on February 21 2008 in hard copy.
- Further revisions by the review division dated February 21, 2008.
- Arcalyst Patient Package Insert (PPI) version 1.14.1.3, submitted May 25, 2007.

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 9.1, and a Flesch Reading Ease score of 55.6. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised PPI has a Flesch Kinkaid grade level of 8.0 and a Flesch Reading Ease score of 62.5%.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. A PPI for rilonacept is voluntary. Except where drug or biologic products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly likely that patients will receive the PPI. The sponsor should state their mechanism for intended distribution of the PPI to patients.

2. We are aware that based on comments by DMETS in their October 24, 2007 review, that the sponsor has submitted a proposal

They also propose

We have the following comments:

- The Patient Package Insert contains Patient Instructions for Use. The Patient Instructions for Use are very cumbersome and should be simplified. The term "reconstitution" is not patient-friendly.

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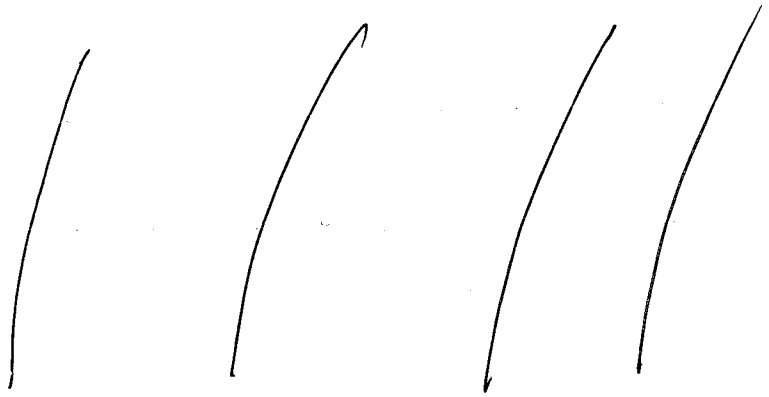

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- Of note, the sponsor proposes that the patient will need to bring their vials of ARCALYST and ancillary supplies to their healthcare provider's office for initial dosing. We are concerned that patients may and attempt to inject their medicine without proper training by their healthcare provider.

- The sponsor's proposed plan does not address the DMETS concern of having a larger dose of drug in each vial than what is approved for the indicated use. Given that the product is intended to be "self-administered" by the patient or a caregiver, there is potential for dosing errors. The sponsor needs to more clearly address this issue in the Patient Package Insert and Patient Instructions for Use.

3. The sponsor uses the terms "healthcare professional" and "healthcare provider" in the proposed PPI and Patient Instructions for Use. We recommend using the term

"healthcare provider" throughout both documents. The term "healthcare professional" is vague and should not be used in patient materials.

Please let us know if you have any questions.

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_____ Deliberative Process

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
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Date: October 29, 2007

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

Thru: Gerald Dal Pan, M.D., M.H.S., Director
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29Oct07

From: **OSE Rilonacept Risk Management Team**
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Subject: Review of proposed Risk Management Plan

Drug Name(s): Arcalyst (rilonacept)

Application Type/Number: 125249

Applicant/sponsor: Regeneron Pharmaceuticals

OSE RCM #: 2007-1469

EXECUTIVE SUMMARY

Rilonacept is an interleukin-1 (IL-1) antagonist. Regeneron Pharmaceuticals is proposing rilonacept for — treatment ——————— of Cryopyrin Associated Periodic Syndromes (CAPS) such as Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Regeneron Pharmaceuticals has identified the following risks associated with rilonacept: injection site reactions, infections, drug-drug interactions (concomitant use with live vaccines, TNF inhibitors), hypersensitivity reactions, and malignancies. To manage these risks, the Sponsor proposes labeling, routine pharmacovigilance, and ——————. We have provided recommendations on all three of these components.

The proposal does not constitute a formal risk minimization action plan (RiskMAP). DAARP and OSE have not identified any additional safety concerns for rilonacept that warrant consideration of a RiskMAP at this time for the proposed indication. However, we do note that the risk of medication error resulting from self-administration has not been addressed. Patient education regarding how to properly prepare and administer rilonacept for subcutaneous injection is crucial and can occur outside of a RiskMAP.

Should rilonacept be considered for approval for additional indications or significant off-label use is identified, the need for a RiskMAP may need to be re-considered based on the risk benefit profile and any evolving safety information.

1 BACKGROUND

1.1 INTRODUCTION

This review follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) to review and comment on the proposed Risk Management Plan (RMP) for ARCALYST (rilonacept) lyophilized powder for injection dated May 29, 2007, and submitted to OSE for consultation on June 29, 2007.

Regeneron Pharmaceuticals is proposing rilonacept for — treatment, ——————— of Cryopyrin Associated Periodic Syndromes (CAPS) such as Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). The proposed indication does not include Neonatal Onset Multisystem Inflammatory Disease (NOMID), the third disease included in the triad of autosomal dominant hereditary febrile syndromes, known as CAPS.[1] All three diseases are caused by mutations in *CIAS1*, the gene encoding cryopyrin which regulates IL-1β production. CAPS is characterized generally by localized and systemic inflammation, including overproduction of serum amyloid A, increased production if IL-1β. More specifically, FCAS patients develop chills, fever, headache, arthralgia, conjunctivitis, and an urticaria-like rash in response to generalized cold exposure. In MWS there is a similar rash, but it is not usually induced by cold. MWS patients also develop fevers, abdominal pain, limb pain, arthritis, conjunctivitis, and, over time, sensorineural hearing loss. NOMID is the most severe of the three disorders, with chronic aseptic meningitis, a characteristic arthropathy, and urticarial rash.[1]

Rilonacept is an interleukin-1 (IL-1) antagonist. It is a fusion protein consisting of both human IL-1 receptor components (IL-1R1 (type 1 receptor) and IL-1 receptor accessory protein) required

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[1] Kasper DL, Fauci AS, Longo DL, Braunwald E, Lauser S, Jaeson JL (Eds.). Harrison's Principles of Internal Medicine. (16th Ed). United States. The McGraw-Hills Companies.

for IL-1 signaling and the Fc portion of human immunoglobulin G1. Thus, rilonacept blocks activation of IL-1, a cytokine that is thought to be overproduced in patients with CAPS.

1.2 REGULATORY HISTORY

Rilonacept has not been studied outside of the United States. It has been studied under – IND – (1) autoinflammatory diseases (CAPS. Rilonacept is an orphan drug and received fast track designation on May 3, 2006, for this indication. CAPS is an orphan disease that affects approximately 500 people in the United States. Because of the limited population, the Phase 3 clinical studies (Study IL1T-AI-0406 (n=5) and Study IL1T-AI-0505 (n=59)) could only be conducted in a small number of patients. At the time of BLA submission, the safety database was comprised of over 500 subjects who have been exposed to rilonacept through 14 Phase 2 and Phase 3 studies for various indications) for up to two years. Currently there are no FDA-approved treatments for CAPS.

Kineret (anakinra) is the only approved interleukin-1 antagonist (FDA approved November 14, 2001). Anakinra is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs.[2] The Sponsor notes that anakinra is a once daily subcutaneous injection while rilonacept is a once weekly subcutaneous injection.

2 METHODS AND MATERIALS

The following materials were reviewed:

- Fava W. DMETS consultation response [draft] dated October 22, 2007.
- Proposed prescribing information for Arcalyst (rilonacept) submitted October 3, 2007, by Regeneron Pharmaceuticals.
- Safety Specification and Pharmacovigilance Plan (for) Rilonacept (IL-1 Trap) submitted June 29, 2007, by Regeneron Pharmaceuticals.
- Kineret (anakinra) approval letter dated November 14, 2001.
- Kineret (anakinra) Package Insert. Amgen; 2001.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

The Sponsor has – ongoing or completed studies involving approximately 550 patients (healthy volunteers or patients with various diseases) being treated with rilonacept.

An initial open-label study (IL1T-AI-0406) involving five patients with CAPS was completed by the NIH. These patients have been treated for approximately two years.

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[2] Kineret Package Insert. Amgen; 2001.

[3] FDA internal team meeting on September 13, 2007.

The "pivotal" Phase 3 multi-center study (IL1T-AI-0505) for CAPS included a total of 59 subjects. Forty-seven patients participated in Part A (3-week screening period, 6-week double-blind, placebo-controlled phase) and Part B (9-week single-blind, active treatment followed by a 9-week, double-blind, placebo-controlled randomized withdrawal phase). An additional 12 patients (including 4 pediatric patients ranging in age from 5-18 years old) were enrolled in the 24-week open-label, extension phase.

The Sponsor states that across all studies 28 subjects reported a total of 49 serious adverse events (SAEs). Of these, 6 events were reported during the screening period, leaving 43 treatment emergent (TE)-SAEs. Thirty-six of the 43 TE-SAEs occurred in patients treated with rilonacept. Five events (involving 3 unique patients) were viewed by the principle investigator to be related to rilonacept as follows:

- Atypical mycobacterial infection
- Gastrointestinal hemorrhage
- Colitis
- Sinusitis
- Bronchitis

The Sponsor does not provide a summary of these 5 TE-SAEs or provide a summary of the 36 reported TE-SAEs in this submission.

3.1.1 Sponsor's Safety Concerns

The Sponsor states that

> [n]o significant safety issue associated with the use of rilonacept has been identified in the studies that have been completed. Furthermore, no pattern of SAEs has emerged during testing of rilonacept in subjects with CAPS, and the AEs that have been observed have been relatively mild to moderate in nature. Of all the AEs reported, only injection-site reactions and infections were found to occur at a higher frequency in the study population.

The Sponsor has identified the following risks for further evaluation:

- Injection site reactions
  - Study IL1T-AI-0505: During the 48 week study, injection site reactions including erythema, pruritis, and swelling were reporting in 45 (76%) patients. The incidence in placebo was not provided. The reactions were characterized as mild in severity.
  - All studies: Across all studies, injection site reactions (i.e., erythema, irritation, pain) were the most commonly reported TEAEs, reported by 45% of subjects treated with rilonacept compared to 30% of subjects treated with placebo. Most reported were assessed as mild in severity.
- Infections
  - Study IL1T-AI-0505: During Part A, infection was reported more frequently for rilonacept-treated subjects (11 (48%)) compared to placebo (4 (17%)). In particular, upper respiratory tract infections were reported most frequently (26% vs 4% placebo). Over the entire 48-week study period, the Sponsor states that the incidence of infection was similar (actual numbers not provided). The Sponsor does not provide any detail about the infections, timing of infection in relation to the study. This may be an important detail because of the nature of

the study design (crossover, re-randomization, etc...) and drug pharmacokinetics (terminal $t_{1/2}$ 8.6 days).[4]
    - All studies: Across all studies, infections were the second most commonly reported TEAE with an incidence of 34% compared to 27% in placebo.

The Sponsor acknowledges the following as potential risks for further evaluation:

- Drug-drug interactions:
    - No drug interaction studies have been conducted with rilonacept.
    - The Sponsor recommends that live vaccines not be administered concurrently with rilonacept unless the potential benefit outweighs the risk. This issue could prove particularly challenging if the drug is used in pediatrics.
    - The Sponsor recommends that tumor necrosis factor (TNF) inhibitors are not administered concomitantly with rilonacept due to the probable increased risk of serious infection.
- Hypersensitivity: The Sponsor states that hypersensitivity reactions have been "rare" but fails to further characterize the cases and risk.
- Neoplasms: At the time of this submission, the Sponsor states that two malignant neoplasms have been observed in rilonacept-treated patients. It is not clear if this information is across all studies or specific to CAPS patients. These malignancies were identified within 3 and 9 weeks of initiating rilonacept. According to the Sponsor, both subjects had "significant risk factors for developing neoplasms and possibly pre-existing disease prior to initiation of rilonacept." One event was described as "recurrent basal cell carcinoma." No other information was provided on the second neoplasm.

3.1.2 DAARP Safety Concerns

In an internal team meeting on September 13, 2007, DAARP stated that the risk of infection, injection site reactions, and immunogenicity were being explored and, at present, the medical officer had not found anything of significant concern to require risk minimization measures beyond labeling and routine pharmacovigilance. At that time, DAARP was awaiting response on an information request for data to determine if there is a possible association between when immunogenicity develops and injection site reactions. DAARP expressed interest in gaining more information on the effects of rilonacept on reproductive health given the chronic nature of the disease and potential need for long-term rilonacept treatment. There was some discussion regarding the potential for off-label use and DAARP shared . Drug cost and reimbursement were discussed as being potentially prohibitive to off-label use.

In an internal team meeting on October 4, 2007, DAARP stated the 120 day safety update provided by the Sponsor presented no new safety concerns, no additional SAEs or opportunistic infections. The medical officer reported no evidence of increased incidence of upper respiratory infections during the second winter. Further, the Sponsor responded to the DAARP request for data on immunogenicity regarding a possible association with injection site reactions. No pattern or trend was elucidated.

3.1.3 OSE Safety Concerns

OSE has not identified any additional safety concerns for rilonacept that warrant consideration of a Risk Minimization Action Plan (RiskMAP) at this time for the proposed indication. However,

[4] Regeneron's proposed PI submitted October 3, 2007.

we do note that the risk of medication error resulting from self-administration has not been addressed.[5] The Sponsor does not explain how patients and/or caregivers will be educated on how to properly prepare and administer the product. In absence of educational materials directed at patients and caregivers and/or a patient package insert[6] outlining the supplies needed (i.e., sterile water for injection, needles) proper reconstitution technique, and proper administration techniques; rilonacept may pose a significant risk of medication error. This risk needs to be mitigated through appropriate education/instruction which can occur outside of a RiskMAP.

Further, based on the adverse events reported in the rilonacept clinical trials, as well as what is known about the safety profiles of other therapeutic biologic products, it seems prudent to continue to actively pursue long term safety information.

3.2 PROPOSED RMP

The Sponsor proposes routine and additional pharmacovigilance activities to continue to monitor the identified and potential risks discussed previously. Regeneron proposes routine labeling to minimize the risks noted in the clinical trials. They propose to employ both passive (spontaneous reporting) methods of safety surveillance.

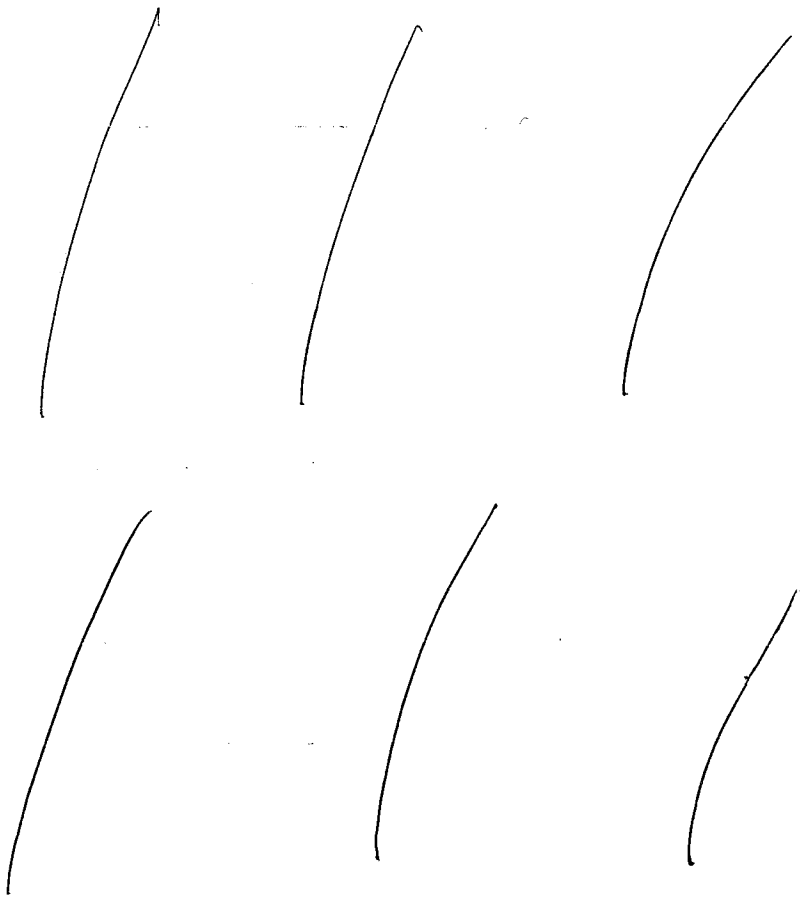
- **Labeling**: The labeling proposed by Regeneron includes

- **Passive Surveillance**:
  - Establish toll-free number: The toll-free number will serve) collect safety information, The telephone operators will be "appropriately trained."
  - Establish rilonacept website: The website will contain
  - Include the mailing address for Regeneron for rilonacept- n the full prescribing information,
  -

[5] Fava W. DMETS consultation response [draft] dated October 22, 2007.

[6] We note that the risk management proposal mentions a PPI but it has not been submitted to FDA for review.

- Submit Periodic Safety Update Reports (PSURs): Regeneron will submit PSURs on a quarterly basis for the first 3 years after approval and then on an annual basis unless more frequent reporting is requested by FDA



The safety profile compiled from all the above methods will be continually monitored for increased frequency of AEs, trend analysis, and signal detection.

4 DISCUSSION

Risks such as infection and malignancy are well-known risks associated with therapeutic biologics and are not unique to rilonacept or unexpected given its effect on the immune system. Based on the information provided by the sponsor and discussion with DAARP, it does not appear at this time that these risks occur with substantially more or unexpected frequency or severity with rilonacept. However, bear in mind that the limited number of patients exposed to rilonacept (64 CAPS, ~500 patients, overall) for a relatively modest exposure time may significantly influence the assessment of safety.

The risk management proposal for rilonacept is consistent with those of routine risk minimization activities such as labeling and incorporates both routine and additional pharmacovigilance activities. The following provides a discussion of these components, and where applicable, a comparison to anakinra, the only other IL-1 antagonist marketed currently.

Labeling

anakinra included certain post-marketing comments.[7] While such studies may not be feasible at this time for rilonacept given the expected limited population, these types of studies may warrant consideration in the future if rilonacept is approved for broader use.

5 CONCLUSION

The Sponsor's proposal includes routine and additional pharmacovigilance activities including a registry to collect ongoing safety information. They also propose only routine labeling to minimize known risks; therefore, the proposal does not constitute a formal RiskMAP. The risks identified by the Sponsor – injection site reactions, hypersensitivity reactions, and infections – are typically managed through routine pharmacovigilance activities consistent with the plan outlined by the Sponsor. Other adverse events such as malignancy and immunogenicity are also expected (and significant) with products that effect the immune system. Based on the information provided, this approach seems reasonable at this time. Should rilonacept be considered for approval for additional indications or significant off-label use is identified, the need for a RiskMAP may need to be re-considered based on the risk benefit profile and any evolving safety information.

Patient education regarding how to properly prepare and administer rilonacept for subcutaneous injection should be addressed and materials should be available at the time of product launch. This education could occur outside of a formal RiskMAP.

Should DAARP raise further concerns with the risks outlined above or identify additional risks associated with rilonacept warranting more extensive risk management activities or a formal RiskMAP, please send a consult to OSE Risk Management Team.

6 RECOMMENDATIONS

- Create educational materials directed to patients and/or caregivers to provide proper reconstitution and administration instruction. This education can occur outside of a formal RiskMAP.
- Labeling
  - At minimum, the label should state, "The impact of treatment with rilonacept on the development of malignancies is not known." The current proposed text

[7] Kineret (anakinra) approval letter dated November 14, 2001 (in pertinent part):

- To submit data from an ongoing study to assess the long-term safety of Anakinra.
- To conduct an eight-week controlled, randomized study to evaluate the safety and efficacy of vaccination while on Anakinra therapy.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process