

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BL 125249/0

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	February 27, 2008
From	Curtis J Rosebraugh, MD, MPH Acting Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	125249
Supp #	
Proprietary / Established (USAN) Names	Rilonacept Arcalyst
Dosage Forms / Strength	Lyophilized powder for reconstitution 160 mg subcutaneous injection every week for adults 2.2 mg/kg subcutaneous injection every week for children
Proposed Indication(s)	For the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.
Action:	<i>Approval</i>

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action on rilonacept and I refer the reader to the reviews in the action package for a more detailed discussion. Regeneron is seeking licensing approval under the orphan drugs provisions (CFR 316) for the biologic Rilonacept, which is for use in Cryopyrin-Associated Periodic Syndromes (CAPS). Cryopyrin is a protein component of inflammasome which activates caspase 1 and results in the release of interleukin-1 β . The pathogenesis of CAPS is believed to be related to uncontrolled overproduction and release of IL-1 with resultant inflammation. As is outlined in Drs. Rappaport, Siegal and Burkhart's reviews, CAPS is a rare disease, affecting approximately 200 to 300 people domestically, and is composed of three distinct autoinflammatory diseases that are characterized by mutations in the gene responsible for the production of the protein cryopyrin. The three autoinflammatory disorders comprising CAPS are:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal Onset Multisystem Inflammatory Disorder (NOMID)

There are common features to all three that include chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonuclear leukocytosis with organ infiltration. Of the three, NOMID is the most serious, presenting early in life with severe dermatologic, rheumatologic and neurologic manifestations, while MWS is associated with sensorineural deafness and an increased risk of amyloidosis and FCAS is characterized by urticaria-like skin lesions, swollen and painful joints, conjunctivitis and fevers following exposure to cold.

Riloncept is a fusion protein that is designed to work as a soluble decoy receptor that binds to, and neutralize the effects of, IL-1 β and IL-1 α . At present, there are not any approved products to treat CAPS, although the IL-1 blocker anakinra is used on a daily basis subcutaneously as off-label therapy. The action on this application for Riloncept will provide for an approved therapy which is used on a once weekly (subcutaneously) basis. Since there are not any approved therapies, Riloncept received a priority review.

Perhaps the most challenging aspect of this application was the CMC product quality review.

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As such, assuring quality of drug substance and product proved to be very challenging. However, the issues that would prohibit approval have been resolved and Dr. Fuchs has outlined a number of post-marketing commitments/agreements that the sponsor has agreed to.

Regarding the nonclinical pharmacology /toxicology, I agree with Dr. Rappaport's assessment regarding approval in adolescents. There was some debate among the team regarding whether Riloncept should be approved for use in children due to some hormonal and bone growth deformity changes that were found in reproductive toxicity studies. After further consideration, it was felt that these findings could be clearly denoted in the product labeling and when viewed in the light that the animal findings may not be translatable to the clinical setting and that this product will have its most important impact on the pediatric patients, it was felt that Riloncept should be approved for pediatric patients. I agree with that line of reasoning. I also think that it is reasonable to request further juvenile non-clinical and clinical testing as post-marketing commitments to further define labeling.

As far as labeling for a pediatric population however, we do not have exposure pharmacokinetic data for adolescents or children under the age of 13 in this submission. We also plan on asking for a postmarketing commitment to perform pharmacokinetic (PK) studies in children. As such, I would limit the dosage age range to 12 years old and above in this labeling pending further PK data. The sponsor has indicated

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Riloncept has a T_{max} of about 3 days and a T_{1/2} of 6 days during SC administration. Absolute bioavailability was about 43%. During the clinical pharmacology/biopharmaceutics review it was noted that there was not any dose ranging studies for this compound. Due to the limited population with CAPS, designed adequate dose ranging would be quite challenging. The applicant chose a dosing regimen based on calculations to completely bind expected

qualities of IL-1 molecules and receptors. Due to the challenges associated with further defining dose ranging, this approach is probably adequate, but consideration could be given clinically to whether lesser dosages, or a longer dosing interval, would have lesser side effects while retaining efficacy. Also noted during the development was that approximately 41-43% of the riloncept treated population had binding antibodies to the receptor portion of the molecule with a small number developing neutralizing antibodies. However the antibody titers were low and fluctuated over time and there was no clear association between anti-riloncept antibodies and either loss of efficacy or any safety findings.

The limited number of patients with CAPS disease made designing a clinical program to demonstrate efficacy challenging. In close collaboration with the Division, the sponsors designed a single pivotal trial that was felt might provide convincing evidence of efficacy. The pivotal trial had two parts including two separate randomizations. For the first part, there was a 21 day screening and baseline period where subjects produced a composite score on a 0-10 scale of five key disease symptoms:

- 1) feelings of fever/chills
- 2) rash
- 3) eye redness/pain
- 4) fatigue
- 5) joint pain

The primary endpoint was a reduction in mean disease activity at six weeks (averaged over last 21 days of therapy). The results demonstrated a change in treated patients of -2.6 compared to placebo patients of -0.3 with $p < 0.0001$.

For the second part, all subjects received active agent for nine weeks and then had a randomization withdrawal to either riloncept or placebo so that disease activity of those remaining on active agent could be compared to those being switched to placebo. After randomization, the mean scores of the placebo group increased from 0.2 to 1.2 for a change (increase) in disease activity of 0.9, compared to no change in those remaining on riloncept with $p < 0.0001$. These results provided clear and convincing evidence that riloncept has efficacy in the treatment of CAPS. It should be noted that the placebo group disease activity had not increased to baseline levels after 21 days, which may be because this portion of the study was conducted during the summer months when symptoms would be expect to be at their mildest (this was done to demonstrate that using riloncept in the summer would still provide a clinical benefit) or that the dosing interval could conceivably be increased. The efficacy results are summarized in the table below from Dr. Rappaport's review.

Primary Analysis for Study IL1T-AI-0505.

STUDY PHASE	TIME POINT	RILONACEPT MEAN +/- SD	PLACEBO MEAN +/- SD	COMPARISON P-VALUE*
Part A:		N=23	N=24	
	Baseline	3.1 +/- 1.9	2.4 +/- 1.5	
	Endpoint	0.5 +/- 0.5	2.1 +/- 1.5	
	Change	-2.6 +/- 1.9	-0.3 +/- 0.7	<0.0001
Part B:		N=22	N=24	
Single-Blind	Baseline	0.5 +/- 0.5	2.1 +/- 1.5	
	Endpoint	0.3 +/- 0.3	0.3 +/- 0.4	
	Change	-0.2 +/- 0.4	-1.8 +/- 1.4	
Part B:		N=22	N=23	
Withdrawal	Baseline	0.3 +/- 0.3	0.2 +/- 0.4	
	Endpoint	0.4 +/- 0.5	1.2 +/- 1.0	
	Change	0.1 +/- 0.4	0.9 +/- 0.9	0.0002

The safety database is limited as would be expected for a drug used to treat such a limited population. The safety exposure in CAPS patients is supplemented to some extent by some exposure in patients with rheumatoid arthritis. The main adverse event that was noted was injection site reactions, however I would expect that this product will have most of the adverse events common to immune modulators. The main, but not only, concern is infection as this drug does affect a key cytokine in mediating host defenses. One could also speculate that, as with most immune modulating drugs, riloncept could pose an increase risk for malignancy.

My final comments are regarding a Division of Medication Errors and Technical Support review From Linda Y. Kim-Jung that, while dated as February 21, 2008, was received by e-mail at 5:20 PM on Tuesday, February 26, 2008, the day before the action date. This review recommends a non-approval action for potential/theoretical misuse issues that I will discuss below.

To develop the background for DMETS concerns, it is important to understand that riloncept comes as a lyophilized product containing 220 mg of interleukin-1 in a single-use vial that requires reconstitution with 2.3 mL sterile water for injection. From this 2.0 mLs (160 mg) are to be withdrawn and injected (at least in adults-adolescents will require dosage based on weight). It is envisioned that this product would be reconstituted and injected by the patient, or a health-care giver, after adequate training by the physician. It is my understanding that the clinical trials included a similar type program (with one difference discussed below), and that there were not any safety issues demonstrated, although this was in a limited population. DMETS concerns stem from whether this data can be transferred to real world setting when considering one difference in the trial setting compared to the proposed distribution plan. It should also be noted that this product is for use in a very limited number of patients. It is also important to note that the clinical/products teams do not agree with DMETS concerns.

I would just state before reviewing the issues developed by DMETS in detail, that a tension always exists regarding when to delay approval of a product, particularly a product such as this one that has proven very effective in a disease where there are not any other approved therapies, in order to allaying any possible theoretical concerns. These decisions tend to be very difficult as the issues may reflect differing groups or personal opinions/gestalt and may not have data to inform a decision. This can be particularly relevant when the issue involved the adequacy of labeling or training which can appear different to the eye of each beholder. As with any decision there is always a risk/benefit calculation to be incorporated, in this case, it is whether a delay is warranted for the concern over whether there will be drug administration problems, particularly when suggested remediation's may have not been tested, and what data we do have, previous precedence and clinical trial information, do not sound an alarm.

The sponsor is proposing that the patient will acquire the product, which will contain _____ as well as the approved labeling (including a patient informational sheet) detailing the disease and how to use the product, and then return to the physician's office for training on preparation and self-injection. It is conceived that this will be a one-time training encounter. This is different from the clinical trial, where the physician had the product initially and therefore the patient could only get the product by going for the training visit to physician, assuring that the patient received training. DMETS has two concerns in this regard, one is that a single patient visit will not be adequate, and the second is that _____ may tempt some patients to try to reconstitute and inject the product without the physician visit. DMETS feels that the product should only be available to the physician, forcing the patient to go to the doctor's office to receive it, thus assuring that they receive adequate instruction. I should also note that the DMETS review states that the _____

I also think that limiting the medication to the physician only involves a new distribution system, which I'm not sure we can mandate, but is also overly paternalistic. I would also state, that if a patient or care giver does not feel confident to perform the tasks required for their own injection after one physician visit, nothing in the sponsor's program prohibits another visit to the physician. It is also instructive that the clinical trials included one instructional session that seems to have been adequate. I also think that one could make a case that it would be useful for the patient to receive the product and instructional material prior to a physician visit, to help the patient/care giver review what will be required of them and to help them develop questions to ask the physician. One final point for consideration is that the agency has had other injectable lyophilized products in the past, which have required similar preparation as this one, and has not required the type of program suggested by DMETS where the product was distributed only through the physician. This includes Embrel, which arguable should have the same concerns as this product, yet none of these concerns materialize after approval.

The other issue was that the vial, once reconstituted, will have product in it in excess to the required dose. As noted in Dr. Rappaport's review, it is felt that this is not an issue as the

reconstituted product is too viscous to allow total extraction, and the safety of the product is such that even if this were accomplished, there should not be an untoward outcome from an additional 60 mgs of product.

To summarize, while I appreciate and have considered the views of DMETS, I do not agree with delaying marketing of this important product. While there may be administration errors associated with use of this product, it may be that no program would prevent such errors, and the suggestions of DMETS for remediation are not tested, can be questioned in their own right, and we have some prior experience to draw upon that does not seem to have been concerned by DMETS (or at least not articulated in the latest review). I must weigh how long to delay availability of this very valuable therapy while contemplating programs, that will also be untested, and if those delays are warranted. Also in that consideration must be that this is for a very limited population, where if errors occur we should be able to discover it quickly and adjust accordingly. In weighting all this different considerations, I do not find DMETS conclusions or recommendations to carry enough weight to delay the marketing of rilonacept or to warrant changes in their distribution plans at this time.

2. Conclusions and Recommendations

This application is for an indication that affects a very limited group of patients. Data from the randomized clinical trial provided convincing evidence of the efficacy of rilonacept in the treatment of two of the three autoinflammatory disorders comprising CAPS. The safety database is limited and vigilance will have to be high to determine if rilonacept has a severe adverse event not expected with immune modulators, or if severe adverse events occur at higher rates than other immune modulators. The safety data in children is very limited and as such patients in the pediatric age range should be followed very closely. I agree with the review team that rilonacept should be approved for the treatment of CAPS as noted above pending agreement on labeling, other outstanding issues and post-marketing commitments.