

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BL 125249/0

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)**

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THROUGH: Linda Kim-Jung, Pharm D., Team Leader *LMK 11/16/07*
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FROM: Walter Fava, R.Ph., Safety Evaluator *Walter Fava 11-16-07*
Division of Medication Errors and Technical Support, HFD 420

PRODUCT NAME:

Primary Name: Arcalyst®
(Rilonacept) Lyophilized Powder for Injection
220 mg vial

BLA #: 125249

SPONSOR: Regeneron Pharmaceuticals, Inc

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Arcalyst®. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document. Additionally, a Risk Management Plan was submitted which will be reviewed under separate cover.
2. DMETS recommends the implementation of the label and labeling revisions outlined in section III of this review in order to minimize user errors and maximize the safe use of this product.
3. DDMAC finds the proprietary Arcalyst acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryl Wiseman, Project Manager, at 301-796-0567.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
(DMETS; White Oak 22, Mail Stop 4447)
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: August 24, 2007
BLA NUMBER: BL-125249
NAME OF DRUG: Arcalyst®
(Rilonacept) Lyophilized Powder for Injection
220 mg vial
IND SPONSOR: Regeneron Pharmaceuticals, Inc

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170), for a re-assessment of the proprietary name, "Arcalyst®" regarding potential name confusion with other proprietary or established drug names. DMETS initially found the name acceptable in OSE Review 2006-252 dated September 8, 2006. The sponsor also provided container labels, carton, and patient information for review and comment. An independent name analysis conducted by _____ was forwarded for review and comment. Furthermore, a Risk Management Plan was submitted for this product. However, any Risk Management Plan concerns or comments will be forwarded to the Division under a separate cover OSE Review #: 2007-1469.

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.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Arcalyst to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

An overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Arcalyst. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Arcalyst, acceptable from a promotional perspective.
2. Since the previous review, the Expert Panel identified two additional proprietary names, Adalat and Orlistat, that were thought to have the potential for confusion with Arcalyst.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

B. SAFETY EVALUATOR RISK ASSESSMENT

1. Product Safety Concerns

In our previous review, we were not provided an opportunity to review the labels and labeling, thus we could not evaluate the potential for error with the use of the product. However, in this review, we were able to assess the potential for medication errors with the use of this product. DMETS analyzed the proposed packaging, label, and labeling in addition to reviewing the name. Our analysis of package configuration, label, and labeling, identified the following failure modes.

a. Volume to Administer

Arcalyst will be packaged in single use vials, each containing 220 mg of lyophilized powder, which is a dose greater than is recommended for subcutaneous injection. In section 11 of the package insert, "Description", it states that each vial of Arcalyst is to be reconstituted with 2.3 mL of Sterile Water for Injection and that each vial contains 220 mg rilonacept (160 mg/2 mL after reconstitution). In addition, it states that a volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg. DMETS questions whether the physical properties of the drug prevent the remaining 60 mg of solution from being withdrawn from the vial, or whether it is possible to withdraw the total labeled 220 mg dose from the reconstituted vial? DMETS has requested this information from the review division, but the answer from the sponsor is still pending.

A consequence of having a larger dose of drug in each vial than what is approved for the indicated use, is the potential for overdose or improper dosing of the product. Given this risk, DMETS believes that the sponsor should propose a vial size and/or concentration which is more conducive to the end user in order to mitigate the potential for administration and dosing errors, especially in the light of the proposed labeling which indicates that this product is to be a _____ by the patient or the caregiver (see section b below).

b. Preparation Errors

Another safety concern is the potential for patients to be prescribed Arcalyst for use at home without the proper supplies (i.e., sterile water for injection and needles). This is especially concerning because the product is not co-packaged with the sterile water for injection which is needed for reconstitution. In clinic settings or when home health care nurses are provided, these issues are not problematic. However, for patients at home who must get prescriptions for Arcalyst filled in retail pharmacy settings, they may encounter numerous problems obtaining the proper supplies. For example, retail pharmacies may not stock vials of sterile water for injection or the correct type of needles and syringes needed to reconstitute, withdraw, and administer this product. Thus, prescribers must ensure that they provide prescriptions for these items to patients when there is self-administration of Arcalyst.

DMETS is unclear as to what the sponsor's distribution strategy is for this product (i.e., will this product only be available in a clinical outpatient setting, home health

care, and/or community pharmacies?). Depending on how this product is distributed, it can impact on how the patients and/or caregivers access the medication and use it properly.

However, regardless of the distribution strategy for this product, DMETS believes that in order to minimize preparation errors in every setting of use, the product should be packaged with all items necessary for the proper reconstitution and administration of the product.

Based on the above safety concerns, DMETS believes that the sponsor should implement an educational campaign for healthcare providers, caregivers and patients to educate them about this product. This plan should provide clear instructions for proper reconstitution and administration of this product. Specifically, if the packaging configuration is not changed to include all the necessary supplies for the reconstitution and administration of this product, then an educational campaign should be implemented to make prescribers aware that they will need to write a separate prescription for sterile water for injection as well as a prescription for needles and syringes. This however, will not solve the problem if the facility does not have the necessary supplies in stock.

2. Arcalyst Name Evaluation

In reviewing the proprietary name Arcalyst, two additional names were identified as having a similar look to Arcalyst. The names include Adalat and Orlistat (see Table 1 below). No names were identified as having sound-alike similarities to Arcalyst.

Table 1: Proprietary Names with Potential for Confusion with Arcalyst

Product Name	Established name, Dosage form(s)	Usual Adult Dose	Other**
Arcalyst	Riloncept lyophilized powder for injection	Inject 160 mg (2 mL) subcutaneously once weekly	
Adalat	nifedipine immediate release capsules: 10 mg and 20 mg	Take 10 mg po tid, maximum dosage is 180 mg /day	LA
Orlistat (established name)	Available as Xenical 120 mg capsule and as Alli 60 mg capsule	Alli 60 mg: Take one capsule three times a day with meals Xenical 120 mg: Take one capsule three times a day with meals	LA
**LA (look-alike), SA (sound-alike)			

- a. Adalat was identified as having look-alike similarities to Arcalyst. Adalat is a calcium channel blocking agent indicated for a number of cardiovascular diagnoses. Although Adalat is no longer on the market, it is available in generic form and prescribers may still order nifedipine immediate release as Adalat.

Adalat may look similar to Arcalyst when scripted. Both names have the same first letter “A”, the same last letter, “t”, and both have the upstroke letter “l” in the middle of their names. However, there are orthographic differences which may help to distinguish this name pair. These differences include the upstroke letter “d” in Adalat which Arcalyst does not have, and the downstroke letter “y” in Arcalyst which Adalat does not have. Additionally, Arcalyst has eight letters compared to the six letters in Adalat, making it appear slightly longer when scripted.

Adalat
Arcalyst

Adalat
Arcalyst

Adalat
Arcalyst

Product characteristics may also help to distinguish Adalat from Arcalyst. Adalat is available as 10 mg and 20 mg oral capsules which are taken three times a day. Arcalyst will be available as a 220 mg lyophilized powder in a vial. The lyophilized powder must be reconstituted with sterile water for injection and is then administered subcutaneously at a usual dose of 160 mg once a week. Additionally, because Adalat is available in multiple strengths, the prescriber would need to indicate the strength. It is also likely that prescribers will need to include specific dosing instructions on all Arcalyst prescriptions in order to ensure patients receive the correct dose at the recommended weekly intervals, which will help minimize orthographic confusion with Adalat. Furthermore, Arcalyst is stored at refrigeration temperatures, whereas Adalat is stored at room temperature, which decreases the potential for product selection errors.

Despite some orthographic similarities between Adalat and Arcalyst, DMETS believes that their different product characteristics will minimize the potential for confusion between the two names.

- b. Orlistat was identified as having look-alike similarities with Arcalyst. Orlistat is the established name for Xenical 120 mg and for Alli 60 mg which are weight loss products used in the treatment of obesity. Xenical is the prescription strength of Orlistat and Alli is the over-the-counter strength of Orlistat.

Orlistat may look similar to Arcalyst when scripted. The first letter "o" in Orlistat may resemble the first letter "a" in Arcalyst when scripted. Both names also contain the upstroke letter "l" and end in the upstroke letter "t". Both names also contain 8 letters which make them appear similar in length when scripted.

Orlistat
Arcalyst

orlistat
arcalyst

orlistat
arcalyst

There are however, orthographic differences which may help to distinguish the two names. Orlistat has three upstroke letters in the following sequence, "l", "t", "t", whereas Arcalyst only has two upstroke letters, "l" and "t". Arcalyst also has a downstroke letter "y" which Orlistat does not have. The dissimilar upstroke and downstroke letter patterns of both names makes them distinct from one another, especially when comparing segments of both names. For example, the last four letters, "stat" of Orlistat look different compared to the last four letters, "lyst" of Arcalyst.

Product characteristics will also help differentiate the two names. Orlistat is available in two capsule strengths, 60 mg and 120 mg and is taken three times a day with meals. Arcalyst however, will be available as a 220 mg lyophilized powder which will need to

be reconstituted before being administered subcutaneously at a dose of 160 mg once weekly.

Prescribing practices may also help to minimize confusion between Orlistat and Arcalyst. Orlistat is available from two manufacturers as two different strengths, and is not available as a generic drug product. Orlistat (Xenical) will not generally be prescribed in an inpatient facility. However, the differences in route of administration between Orlistat and Arcalyst will help differentiate the product in this scenario. With regards to Alli 60 mg, this product is an over-the-counter Orlistat product with considerable direct-to-consumer advertising. Thus, it is unlikely that prescribers will write orders or direct patients to obtain Orlistat. They will most likely use the proprietary name, Alli 60 mg when recommending the OTC product.

Despite some orthographic similarities between Orlistat and Arcalyst, their orthographic differences and lack of overlapping product characteristics should sufficiently minimize the potential for confusion between the name pair.

3. Independent Name Evaluation

The sponsor contracted with _____, to evaluate the proposed proprietary name Arcalyst, for potential confusion with other proprietary drug names. _____ concluded that Arcalyst is acceptable as the trademark for rilonacept.

The study was conducted using 201 practicing physicians and pharmacists. The participants were divided into two groups. One group was given the correct spelling of the name and were then asked to select the intended pronunciation from three choices. The other group was asked to listen to the intended pronunciation and then select the correct spelling of the name from three choices. Both groups were then provided with product characteristic information and asked whether the tradename candidate sounded or looked like any other pharmaceutical product. Additionally, pharmacists reviewed the physicians' handwriting samples on line to identify potential look-alike pharmaceuticals.

Respondents in the _____ survey identified Cytomel, Singulair, Accuhist, as potential sound-alike names with Arcalyst. Respondents also identified Aricept, Cellcept, Orenzia, Allegra, Orlistat, and Aralast as potential look-alike names with Arcalyst. They also identified Mucomyst as having the potential to look and/or sound similar to Arcalyst.

Of these names, Aricept, Cellcept, Orlistat, and Aralast, were evaluated by DMETS and determined either in this review or in OSE review 2006-252, dated September 8, 2006, not to pose a significant risk of confusion with Arcalyst based on lack of convincing look-alike and sound-alike similarities along with lack of overlapping product characteristics.

DMETS did not identify Cytomel, Singulair, Accuhist or Mucomyst as sound-alike names for Arcalyst. DMETS also did not identify Orenzia and Allegra as look-alike names for Arcalyst. After evaluating Cytomel, Singulair, Accuhist, Mucomyst, Orenzia, and Allegra, DMETS finds the potential for confusion with Arcalyst to be minimized by their lack of convincing look-alike and sound-alike similarities in addition to their lack of overlapping

product characteristics such as strength, dosage form, and frequency of administration and/or route of administration.

Overall, DMETS finds the potential for confusion with Arcalyst to be minimized with these names due to lack of convincing orthographic similarities with Arcalyst and lack of overlapping product characteristics such as product strength, dosage form, frequency of administration, and route of administration.

Based on analysis of each of the aforementioned names, DMETS feels the potential risk for confusion with Arcalyst is low, and therefore concurs with the conclusion from _____ that Arcalyst is an acceptable tradename for rilonacept.

III. LABEL, LABELING, AND SAFETY RELATED ISSUES:

DMETS evaluated the container labels, carton labeling, package insert labeling and patient information leaflet for Arcalyst, using failure modes and effects and applying principles of human factors. Our analysis identified the following areas of possible improvement, which may minimize potential user errors.

A. General Comments

1. Arcalyst will be packaged in single use vials, each containing 220 mg of lyophilized powder, which is a dose greater than is recommended for subcutaneous injection. In section 11 of the package insert, "Description", it states that each vial of Arcalyst is to be reconstituted with 2.3 mL of Sterile Water for Injection and that each vial contains 220 mg rilonacept (160 mg/2 mL after reconstitution). In addition, it states that a volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg. DMETS questions whether the physical properties of the drug prevent the remaining 60 mg of rilonacept from being withdrawn from the vial, or whether it is possible to withdraw the total labeled 220 mg dose from the reconstituted vial?
2. In order to minimize medication errors resulting from self-administration of the product, we recommend the following considerations:
 - the product should be packaged with all items necessary for the proper reconstitution and administration of the product.
 - implement an educational campaign for healthcare providers, caregivers and patients to educate them about this product. This plan should include which provide clear instructions for proper reconstitution and administration of this product. Specifically, if the packaging configuration is not changed to include all necessary supplies for reconstitution and administration of this drug, then an educational campaign should be implemented to make prescribers aware that they will need to write a separate prescription for sterile water for injection as well as a prescription for needles and syringes. This however, will not solve the problem if the facility does not have the necessary supplies in stock.

3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process