CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

103950/0

CHEMISTRY REVIEW(S)

Date: September 16, 2000 (Revised November 6, 2001)

To: File (BLA STN 103950)

From: Raymond Donnelly, Ph.D., Division of Therapeutic Proteins

Through: Amy Rosenberg, M.D., Director, Division of Therapeutic Proteins

Subject: Review of CMC/Product Information for BLA STN 103950

Submission File No.: 99-1490

Common Name: Recombinant methionyl human interleukin-1 receptor antagonist (rHu IL-1ra)

USAN Name: Anakinra

Proprietary Name: Kineret™

Name of Manufacturer/Sponsor: Amgen, Inc., Thousand Oaks, CA

I. Pharmacologic Class, Scientific Rationale, Intended Use and Potential Clinical Benefits

A. Pharmacologic Class

Kineret™ (anakinra) is the recombinant form of the human interleukin-1 receptor antagonist (IL-1ra). It is identical to the naturally occurring, non-glycosylated, form of the protein except for the addition of an N-terminal methionine residue. Kineret™ is a 153 amino acid protein with an approximate molecular weight of 17,300 Daltons. The drug product is a sterile, clear, colorless, preservative-free liquid formulated with [redacted] sodium citrate, [redacted] sodium chloride, [redacted] EDTA, [redacted] Tween 80 at pH 6.5 in Water for injection (USP), and is available in prefilled syringes [redacted]

B. Scientific Rationale for the Drug Product

Endogenous, monocyte-derived Interleukin-1 receptor antagonist (IL-1ra) is a naturally occurring inhibitor of Interleukin-1. Interleukin-1 (IL-1) is a key mediator of immune and inflammatory responses. Signaling for IL-1 occurs upon binding of IL-1 to the IL-1 type-I receptor (IL-1RI) found on most cell types. Under normal conditions, serum and other body fluids do not contain detectable levels of IL-1. Interleukin-1 production is induced in response to inflammation, immunologic reactions, microbial invasion, and tissue injury, and may lead to acute or chronic inflammation. IL-1ra has a similar binding affinity to the IL-1 type-I receptor as IL-1, but, is

incapable of transducing a signal. An excess of IL-1ra is needed in order to block the action of IL-1 since a very low level of IL-1 receptor occupancy (2% to 3%) is sufficient to elicit a full response.

In vivo studies with anakinra have shown that IL-1ra can reduce inflammation and joint swelling in animal models of rheumatoid arthritis (RA). Studies of continuous infusion of anakinra in combination with methotrexate demonstrate greater inhibition of rat paw swelling than when either agent is administered individually. In a model of adjuvant arthritis in rats in which anakinra inhibited inflammation only modestly, marked inhibition of bone resorption still occurred.

C. Intended Use

Kineret™ is intended for use in patients 18 years of age or older for the reduction in signs and symptoms of moderate to severe active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS). Kineret™ can be used in combination with

D. Potential Clinical Benefits

Kineret™ has been carefully studied in twelve clinical trials in the rheumatoid arthritis setting. Two large, adequate and well controlled studies have demonstrated that the drug alleviates the signs and symptoms of rheumatoid arthritis as measured by improvements in the American College of Rheumatology criteria (ACR20). Preliminary 6-month data also suggest the drug may slow erosive joint disease as measured by Larssen scores. The major side effect experienced by patients is injection site reactions which, in the majority of patients, are mild and transient. Although infections occur in patients taking Kineret™ their incidence in Kineret™-treated patients is no greater than that observed in placebo-treated patients. Kineret™ thus has the potential for relieving the signs and symptoms of RA, and slowing structural damage to joints with minimal side effects.

II. Chemistry, Manufacturing and Controls Summary

A. Drug Substance

1. Names

The name of the drug substance is recombinant-methionyl human interleukin-1 receptor antagonist or r-metHuIL-1ra. The proprietary name (application pending) is Kineret™ . The United States Adopted Name (USAN) is "anakinra."

2. Physical and Chemical Characteristics

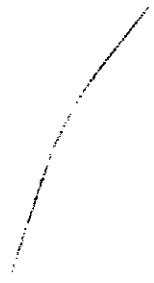
Anakinra is the recombinant form of the human interleukin-1 receptor antagonist (IL-1ra) produced in *E. coli* using recombinant DNA techniques. It is identical to the naturally occurring, non-glycosylated, form of the protein except for the addition of an N-terminal methionine residue. Anakinra contains 153 amino acids and has an approximate molecular weight of 17,300 Daltons. It exhibits 19% and 26% amino acid sequence homology to human IL-1α and human IL-1β, respectively.

Anakinra is a well-characterized recombinant protein. N-terminal sequencing of the protein reveals the lack of formylated or acetylated N-termini or minor sequences. A combined

verified that the protein with the correct sequence was expressed and purified. The purified protein contains The complete sequence of the protein was determined by combining data and matches that expected from the DNA sequence.

studies indicate that anakinra has a well-defined structure and

Purity of the protein is assessed using several



3. Stability

There are — of Filtered Purified Bulk anakinra in the current stability program for this protein. The sponsor states that additional lots will be entered into the stability program when manufactured. Filtered Purified Bulk is tested for purity, potency and integrity using several well defined methods. The program includes studies at the recommended storage condition — , at lower temperatures (-60°C to-80°C), and at controlled room temperature (27°C to 30°C). The specifications that must be met in the stability assays are provided in Table 1. Stability data collected to date support a shelf life of — for Filtered Purified Bulk anakinra.

Table 1. Anakinra Filtered Purified Bulk Stability Assays

Parameter	Specification	Method

4. Manufacturer

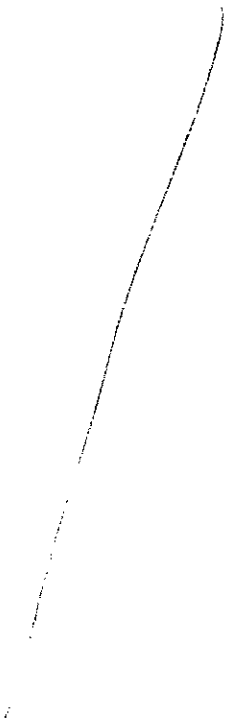
Purified Bulk anakinra is manufactured by Amgen, Inc. at its LakeCentre manufacturing facility in Boulder, Colorodo. This facility is also referred to as: AC 7. The street address of this facility is 5550 Airport Road, Boulder, Colorado.

5. Method of Manufacture

Filtered Purified Bulk anakinra is manufactured in a strain of *E. coli* genetically engineered to optimally express the protein (Amgen strain — during —

Table 2. Specifications and Analytical Methods for Filtered Purified Bulk anakinra

Test	Specification	Amgen Method No.



B. Drug Product

1. Composition of the Drug Product

Kineret™ will be supplied in prefilled syringes containing — 100 — mg anakinra — — The drug product is formulated as a sterile, clear, colorless-to-white, preservative-free liquid with — sodium citrate, — . sodium chloride. — EDTA. — . , Tween 80 at pH 6.5 in Water for Injection, USP. The composition of each of these finished (final) dosage forms in which the drug product will be distributed is provided in Tables 3-6.

*Q.S. = quantity sufficient.

Table 4. Composition of 100 mg Prefilled Syringe

Ingredient	Quantity
IL-1ra	100 mg
Citric acid, anhydrous	1.29 mg
Sodium Chloride	5.48 mg
EDTA	0.12 mg
Polysorbate 80	0.70 mg
Water for Injection	Q.S.*

Note: Formulation buffer is titrated with sodium hydroxide to achieve a pH of 6.5.

*Q.S. = quantity sufficient.

Note: Formulation buffer — to achieve a pH of 6.5.

*Q.S. = quantity sufficient.

2. Manufacturer

Kineret™ will be filled into final product vials and prefilled syringes at Amgen Puerto Rico (APR) located in Juncos, Puerto Rico (US Establishment Registration No.26500228/SJN). Production of final product includes formulation, sterile filtration and filling. APR is currently licensed for the manufacturing of Epoetin alpha (EPOGEN), Filgrastim (NEUPOGEN) and Interferon alfacon-1 (INFERGEN).

Manufacturing Limited (ABML), which is a wholly owned subsidiary of Amgen (Bermuda) Limited (ABL). ABL in turn is a wholly owned subsidiary of Amgen, Inc. ABL has established an operating branch in Juncos, Puerto Rico under the name ABML, and has leased the facilities, equipment and personnel of Amgen Puerto Rico (APR) for the manufacturing of anakinra Final Product.

3. Specifications and Analytical Methods

The specifications and analytical methods used to test the identity, strength, purity and potency of final product anakinra in vials and prefilled syringes are listed in Table 7.

Table 7. Final Dosage Form Specifications and Analytical Methods

Parameter	Specification	Amgen Method No.

****Note: Specifications and analytical methods for the drug product (anakinra) in prefilled syringes are the same as for vials except that a specification for deliverable volume is also included: ≥labeled volume.**

4. Container/Closure System

a. Prefilled Syringes

The selection of the primary packaging materials for manufacturing anakinra prefilled syringes was made on the basis of results of various physical, chemical, and functional tests of the components. The appropriateness of the syringe components was based on the following considerations:

· Syringe integrity against microbiological contamination,
· Compatibility with the formulated anakinra solution,
· Lack of detectable leaching components and
· Breakloose and extrusion properties.

Table 8. Description of anakinra prefilled syringes and syringe components

Component:	Syringe barrel
Supplier	
Material	
Description	
Component	Plunger stopper
Supplier	
Material	
Description	

Component	Plunger rod
Supplier	
Material	
Description	

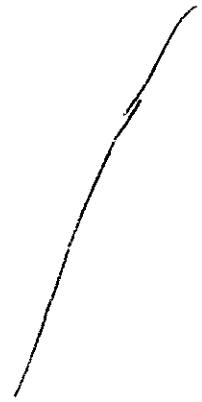
5. Stability

The current stability program for finished product anakinra in vials and prefilled syringes includes lots of finished product in prefilled syringes. The sponsor indicates that additional lots will be placed on stability when manufactured. Finished product ankinra is assessed for integrity, purity and potency when stored at the at the recommended storage temperature of 2°C to 8°C, controlled room temperature (27°C to 30°C), and accelerated temperatures (35°C to 39°C). Additional studies have examined esting of the finished product.

The specifications that finished product ankinra must meet are provided in Table 10.

Table 10. Stability Testing of Finished Product ankinra

Parameter	Specification	Method



Syringes have been stored up to at this temperature.

6. Characterization of the Drug Substance

a. Summary

Biochemical and biophysical analyses were performed to define the primary and higher order structure of IL-1ra and to determine the purity of the product.

b. Primary Structure of IL-1ra

The primary structure of IL-1ra was determined and found to be consistent with that predicted by the DNA sequence. Sequence was determined by a combination of traditional methods that included

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: May 25, 2000

To: File, Reference Number 99-1490 [AMGEN, Inc, License No.:1080]

From: Reginald D. Neal, Reviewer, CBER/OCBQ/DMPQ/MB-1

Subject: Complete Review Memorandum – BLA, Ref # 99-1490 [STN 103950/0]

Approval Recommend -ation

I have completed a review of the Chemistry, Manufacturing and Controls (CMC) sections of the Biologics License Application (BLA) for Anakinra [BLA Reference Number 99-1490]. Based upon my review, I recommend approval of the application. I have no unresolved review issues or questions.

Summary

AMGEN, Inc. has submitted a biologics license application [Reference # 99-1490] for the manufacture of Recombinant Methionyl human interleukin-1 receptor antagonist [IL-1ra], established name –Anakinra. IL-1ra is indicated for the treatment of rheumatoid arthritis. The bulk manufacturing facility is located at the AMGEN LakeCentre facility, 5550 Airport Road, Boulder, Colorado 80301. This BLA was dated 12 January 2000 and was received at CBER January 13, 2000.

The authorized official at the LakeCentre facility is David Bengston, Sr. Director-Site Head, Colorado Operations. As Site-head, Mr. Bengston has designated authority for both the LakeCentre and Longmont facilities. The telephone number at the Boulder/LakeCentre site and for all Amgen Colorado locations is (303) 401-1000. The direct line for Mr. Tim Ornellas, Regulatory Compliance Specialist is (303) 401-7532. The address for the Longmont facility is 4000 Nelson Road, Longmont, CO 80503. The address for Amgen Colorado" administrative headquarters (and mailing address) is Amgen, Inc., 3200 Walnut Street, Boulder, Colorado 80301.

LakeCentre is a new bulk manufacturing facility for the manufacture of [IL-1ra]. This facility is also referred to as AC 7. AMGEN, Inc. currently has assigned biologics license number 1080. The corporate office is located at One Amgen Center Drive, Thousand Oaks, California. The corporate telephone number is 805-447-1000. The responsible agent at the Thousand Oaks location is Jeffery N. Fellows, Director Regulatory Affairs.

The finished product fill operations are performed at the AMGEN Puerto Rico (APR) filling facility in Juncos, Puerto Rico (US Establishment Registration No. 26500228/SJN). Production of final product includes formulation, sterile filtration, and filling. This facility was last inspected on 4/19-30/99 by Team Biologics. The inspection covered formulation, filling, and packaging of currently licensed Epoetin alfa (EPOGEN), Filgrastim (NEUPOGEN), and Interferon alfacon-1 (INFERGEN). An FDA-483 was issued and the final classification was VAI. The next scheduled routine inspection will be in FY 2001. Per information provided by AMGEN, the filling of IL-1ra into syringes will be done or — at AMGEN PR. Based upon the findings of the most recent inspection report, the AMGEN PR facility is not scheduled for inspection for approval of this BLA.

The CMC seven volume submission describes the chemical composition and formula of the drug, the manufacturing processes, and the apparatuses and machinery used.

VOLUME 1 of 7

The IL-1ra protein is the recombinant form of the human interleukin-1 receptor antagonist produced in *E. coli* using recombinant DNA technique.

Stability [Bulk Product] (4.1.1.3)

— lots of filtered purified bulk are currently held in the stability program. Storage temperatures are –20 °C to –40 °C, –60 °C to –80 °C, and room temperature (27 °C to 30°C). Currently stability data supports a shelf life of — for filtered bulk.

In table ***4-1, item 4/vol 1/page 6,*** specifications that must be met in stability assays are listed. These assays include — —

Method of Manufacture

Genetically engineered *E. coli* expresses the protein (Amgen strain . See flow charts ***4-1 & 4-2, item 4/vol 1/page 7 & 8***.

Manufacture is as follows:

Specifications and Analytical Methods tested for filtered purified bulk

C: Upon inspection observe and evaluate the analytical methods used.

Finished Product (manufacture [formulation & filling] @ APR).
To be supplied in syringes , 100 ng volumes)

The drug product is formulated as a sterile clear, colorless-to-white, preservative free liquid with sodium citrate, sodium chloride, EDTA, and Tween 80 [Polysorbate 80] at pH 6.5 in WFI.

Specifications for final dosage forms.

Stability Testing of Finished Product (4.1.2.5)

Currently — — of product pre-filled in syringes.
C: Determine at time of inspection, how many lots have been placed on stability [i.e., manufactured since BLA submission].

Storage conditions tested: recommended storage @ 2 °C to 8 °C [— — , for syringes], controlled temperature @ 27 °C – 30 °C, and accelerated temperature @ 35 °C to 39 °C. Current data supports — for — pre-filled syringes —

C: Upon inspection, find out where the finished product stability samples held and tested.

Characterization of the Drug Substance
C: Upon inspection, find out where the biochemical and biophysical analyses performed [defining the purity of the product]?
Analyses performed:

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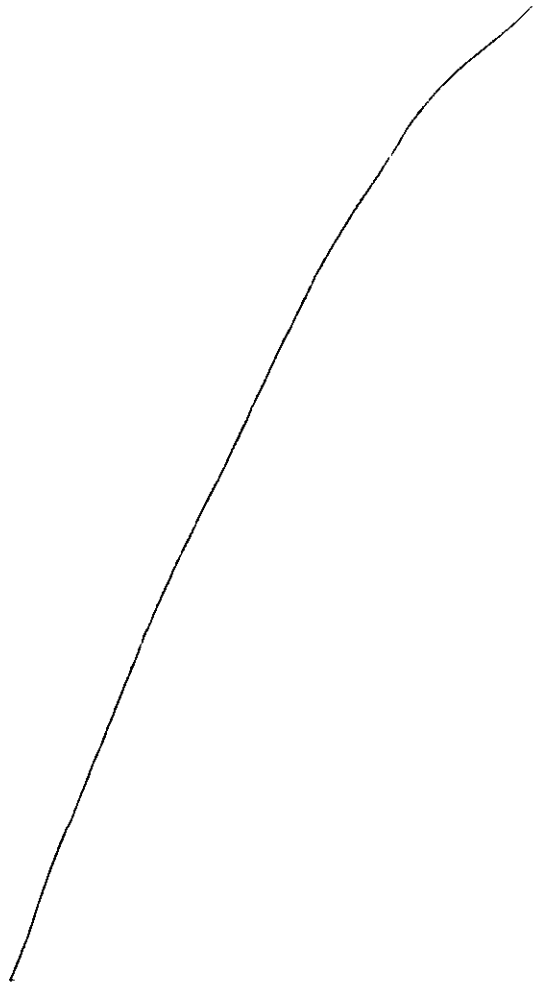
✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



Comments I have reviewed this BLA submission and have no further comments and or questions. Question/Comments documented in the above summary were answered upon inspection. Pending resolution of items listed on the FDA 483 issued 04/20/00, no outstanding inspectional issues remain unresolved.

Review Recommendation

Based upon findings during the application review and inspection of the bulk manufacturing facility at Longmont/ Boulder , I recommend that this application be approved.

Note that an inspection waiver is recommended for the formulation fill site based upon recent inspectional history.

Reginald D. Neal, CBER, DMPQ