CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319Orig1s085, 086, 087

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY sBLA REVIEW AND EVALUATION

Application number:	125319
Supporting document/s:	#0549, 0552, 0554, and 0555 (Supplements #085, 086, 087, and 088, respectively)
Applicant's letter date:	March 23, 2016, March 28, 2016, March 29, 2016, and March 30, 2016
CDER stamp date:	March 23, 2016, March 28, 2016, March 29, 2016, and March 30, 2016
Product:	ILARIS® (Canakinumab; Interleukin-1β blocker)
Indication:	Approved for Cryopyrin-Associated Periodic Syndromes (CAPS) and Active Systemic Juvenile Idiopathic Arthritis (SJIA) Addition of following indications: for Periodic Fever Syndromes that include Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF)
Applicant:	Novartis Pharmaceuticals Corporation Immunology and Dermatology One Health Plaza East Hanover, NJ 07936-1080
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Brandi Wheeler, Pharm.D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125319 are owned by Novartis or are data for which

Novartis has obtained a written right of reference. Any information or data necessary for approval of BLA 125319 that [name of applicant] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125319.

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1 Executive Summary

1.1 Introduction

ILARIS (canakinumab) is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. The Sponsor submitted three efficacy supplements for Periodic Fever Syndromes that include Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF).

A complete response was issued for Supplement #088. A safety assessment of the extractables and leachables data provided in Supplement #088 will be done at a later date; the Sponsor provided a complete response on August 23, 2016.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were provided in these three supplements. The nonclinical Pharmacology and Toxicology studies were reviewed under the original BLA that was approved on June 17, 2009.

1.3 Recommendations

Recommended labeling for Section 13.1 is shown below. A detailed explanation of labeling changes is described later in this review. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

1.3.3 Labeling

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab.

(b) (4)

As canakinumab does not cross-react with rodent IL-1β, male and female fertility was evaluated in a mouse model using a murine analog of canakinumab. Male mice were treated weekly beginning 4 weeks prior to mating and continuing through 3 weeks after mating. Female mice were treated weekly for 2 weeks prior to mating through gestation day 3 or 4. The murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous doses up to 150 mg/kg.

2 Drug Information

2.1 Drug

Tradename: ILARIS

Generic Name: Canakinumab

Biochemical Description: Canakinumab is comprised of two 447-(or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298 (Asn 298).

Pharmacologic Class: Recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass (Interleukin-1β blocker)

2.2 Relevant INDs, NDAs, BLAs and DMFs
IND 100040 (Novartis, Canakinumab)

2.7 Regulatory Background
The BLA was approved on June 17, 2009.

3 Studies Submitted

3.1 Studies Reviewed
No new nonclinical studies were provided in the present supplement.

3.3 Previous Reviews Referenced
Pharmacology and Toxicology Review under the original BLA approval dated June 17, 2009

11 Integrated Summary and Safety Evaluation

ILARIS (canakinumab) is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It was approved for the indications of (1) Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS); and (2) Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

The Sponsor has submitted three efficacy supplements for Periodic Fever Syndromes that include Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF). The indication statements and proposed dosing for each indication are listed below.

- "ILARIS is indicated for the treatment of Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older." The recommended start dose of ILARIS® for TRAPS patients with a body weight greater than 40 kg is 150 mg (or 2 mg/kg for patients with a body weight less than or equal to 40 kg) administered every four weeks.

- "*ILARIS is indicated for the treatment of Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) in adults and children 2 years of age and older.*" The recommended start dose of ILARIS® for HIDS/MKD patients with a body weight greater than 40 kg is 150 mg (or 2 mg/kg for patients with a body less than or equal to 40 kg) administered every four weeks.

- "*ILARIS is indicated for the treatment of Familial Mediterranean Fever (FMF) in adults and children 2 years of age and older in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response*." The recommended start dose of ILARIS® for FMF patients with a body weight greater than 40 kg is 150 mg (or 2 mg/kg for patients with a body less than or equal to 40 kg) administered every four weeks.

The proposed dosing for new indications does not require a recalculation of exposure margins provided in Section 8.1 (Pregnancy).

The nonclinical review of the proposed product label was limited to Section 13.1. The standard battery of genetic toxicology studies is not relevant to proteins produced by recombinant DNA technology.

A complete response was issued for Supplement #088. A safety assessment of the extractables and leachables data provided in Supplement #088 will be done at a later date; the Sponsor provided a complete response on August 23, 2016.

Labeling review:

Below is the recommended text for Section 13.1 after revisions to the Sponsor's proposed label. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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/s/

TIMOTHY W ROBISON
09/06/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA Supplement

BLA Number: 125319 **Applicant: Novartis** **Stamp Date: March 23 (S85), March 28 (S86), and March 29 (S87), 2016**

Drug Name: Ilaris® (Canakinumab) **BLA Type: Supplements**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable (NA) No new nonclinical pharmacology or toxicology studies were submitted. Module 4 was not included. The nonclinical program was reviewed under the initial submission of BLA 125319.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			NA. See comment #1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			NA. See comment #1.
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			NA. See comment #1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA. See comment #1.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			NA. See comment #1.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			NA. See comment #1.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA. See comment #1.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		ACZ885 will be provided as a 150 mg/ 1 mL solution for injection in vial. A safety assessment of extractables and leachables will be performed.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.
NONE

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
NONE

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/s/

TIMOTHY W ROBISON
05/13/2016