CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

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:	May 28, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Carlos M Mena-Grillasca, RPh, Acting Team Leader Denise P. Toyer, PharmD, Deputy Director DP. Toyer 5/28/09 Carol A. Holquist, RPh, Director Carol Holquist 5/28/09 Division of Medication Error Prevention and Analysis (DMEPA)
From:	L. Shenee' Toombs, PharmD, Safety Evaluator L. Toombs 5/28/09 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Ilaris (Canakinumab) for Injection, 150 mg
Application Type/Number:	BLA 125319
Applicant:	Novartis
OSE RCM #:	2009-64

CONTENTS

1 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and insert labeling submitted as part of the April 6, 2009 and April 15, 2009 submissions (see Appendix A and B).

2 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 2.1 *Comments to the Division.* We request the recommendations for the carton and container label in Section 2.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project manager, Chris Wheeler, at 301-796-0151.

2.1 COMMENTS TO THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Title Heading

   Revise the proprietary name, established name, dosage form and route of administration statement to read, "Ilaris (canakinumab) for Injection For Subcutaneous Use Only." Ilaris is supplied as a lyophilized powder that must be reconstituted, thus the dosage form should be presented according to USP nomenclature practices for drug product established names. We recommend you contact the SEALD Team for further guidance on the remainder of the Title Heading in the Highlights Section.

2. Dosage and Administration Subsection

b(4)

B. FULL PRESCRIBING INFORMATION

1. Section 2.2 Recommended Dose

   See comment A2 above

2. Section 2.3 Preparation for Administration

2. Section 2.3 Preparation for Administration
   Section 3 DOSAGE FORMS AND STRENGTHS
   Section 11 DESCRIPTION
   Section 17.5 Information for Patients, Mixing ILARIS and Preparing the injection subsections

   DMEPA recommends against the use of trailing zeroes after a decimal point (e.g., do not use 1.0 mL, use '1 mL' instead) in labels and labeling especially when associated with dosing recommendations. When used with the dose, the number is often misinterpreted which can lead to 10-fold dosing errors (1.0 read as 10). When included in approved labeling, health care practitioners carry this practice over to the prescribing world which may lead to errors. We note that trailing zeroes are used in preparing the admixture (e.g., 1.0 mL) when referring to the diluent . Furthermore, the use of trailing zeroes is included on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] which states they should never be used when communicating medical information. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed to not allow such designations to appear in the approved labeling of products.

2. Section 2.3 Preparation for Administration
   Section 3 DOSAGE FORMS AND STRENGTHS
   Section 17.1 Drug Administration

   The presentation of the diluent for reconstituting Ilaris is inconsistent throughout these sections. We note the diluent is referenced as ' —— b(4)
   —— . DMEPA recommends revising these statements so that a single term is used to represent the diluent. We recommend the use of "Sterile Water for Injection".

3. Section 2.3 Preparation for Administration
   Section 3 DOSAGE FORMS AND STRENGTHS

   Ilaris is presented as a concentration "Ilaris 150 mg/mL powder for ....." When referencing how Ilaris is supplied, remove "/mL" from the presentation of the drug strength. Ilaris is supplied as a 150 mg lyophilized powder. The concentration, 150 mg/mL, applies after the product is reconstituted. The product should be referenced as 150 mg/vial.

4. Section 17.5 Information for Patients

   a. **WHAT ARE THE INGREDIENTS IN ILARIS?** subsection

      i. Modify the statement, "One vial of powder contains 150 mg Ilaris", to read "One vial of powder contains 150 mg of canakinumab" since canakinumab is the active ingredient.

      ii. We note that the other ingredients contain the statement ' —— b(4)
      However, the CMC reviewer has revised this statement in the

[1] http://www.ismp.org/Tools/errorproneabbreviations.pdf, accessed 15APR2009.

DESCRIPTION section of the labeling. This section should also be revised to be consistent with CMC's recommendations since this statement refers to the product before reconstitution.

b. **Information for the health care professional and patients**

Delete the statement "AND PATIENTS" from the heading of this subsection because this product will only be administered by healthcare practitioners.

c. **Instructions for preparing the ILARIS injection**

[redacted] b(4)

The DOSAGE AND ADMINISTRATION section contains directions to the health care practitioners instructing them how to prepare Ilaris.

2.2 COMMENTS TO THE APPLICANT

A. Container Label

1. Revise the drug strength to read "150 mg per vial" or "150 mg/vial" rather than 150 mg/vial. Ilaris is supplied as a 150 mg lyophilized powder. The concentration, 150 mg/mL, applies after the product is reconstituted.
2. Revise the dosage form statement to read, "Ilaris (canakinumab) for Injection. For Subcutaneous Use Only." Ilaris is supplied as a lyophilized powder that must be reconstituted, thus the dosage form should be presented according to USP nomenclature practices for official dosage forms.
3. To provide for additional space for more relevant information, delete the statement [redacted] on the principal display panel. b(4)
4. Add the statement, "See Package Insert for Reconstitution Instructions."
5. Revise the statement "Single Use Vial" to read "Single Use Vial Discard Unused Portion."

B. Carton Label

1. See comments A1 and A2 above and revise the carton accordingly.
2. Relocate the statement, "Store unopened vial .....Do not freeze." to appear before the statement, "See package insert.....Preparation for Administration".
3. Add the statement, "Reconstitute with 1 mL of Sterile Water for Injection. Do not shake. Once reconstituted the solution contains 150 mg of canakinumab per mL." following the statement, "See package insert....Preparation for Administration".
4. The light blue text color over white background is difficult to read on the rear panel. Change the text color to increase the contrast with the white background.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
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Date:	May 29, 2009
To:	Bob Rappaport, M.D. Division Director **Division of Analgesics, Anesthetics and Rheumatology Products**
Through:	Jodi Duckhorn, MA, Team Leader 5/09/09 **Division of Risk Management**
From:	LaShawn Griffiths, MSHS-PH, BSN, RN 5/29/09 Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	ILARIS (canakinumab) injection
Application Type/Number:	BLA 125319
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2009-63

1 INTRODUCTION

Novartis Pharmaceuticals Corporation submitted a New Biological Agent (BLA) 125319 for ILARIS (canakinumab, formerly ACZ885) injection on December 15, 2008. ILARIS is indicated for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS) in adults and children 4 years of age and older. The submission includes proposed Professional Information (PI) in PLR format, with Patient Labeling Information (Patient Package Insert) and Instructions for Use (IFU).

The Division of Analgesics, Anesthetics and Rheumatology Products requested that the Division of Risk Management's Patient Labeling and Education Team review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU). This review is written in response to that request.

2 MATERIAL REVIEWED

- ILARIS Patient Package Insert (PPI) including Patient Instructions for Use (IFU) submitted December 15, 2008
- ILARIS Prescribing Information (PI) submitted December 15, 2008 and revised by the Review Division throughout the current review cycle

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and 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 Applicant has a Flesch Kinkaid grade level of 5.5, and a Flesch Reading Ease score of 75.7%. 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). The reading scores as submitted by the Applicant are acceptable.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- 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. The Patient Instructions for Use (IFU) was not reviewed as this product is not indicated to be given by the patient or caregiver.
2. The Applicant uses both the terms "doctor," and "healthcare provider" in the proposed PPI. We recommend that one term be used consistently throughout the PPI. For this review we have used the term "healthcare provider".
3. Do not use all capital letters in patient information. For better comprehension and to call attention to important information, use other techniques such as bolded font or text boxes.
4. In the "What is ILARIS?" section we removed the disease specific information that can be placed at the end of the PPI after the "Ingredients" section or preferably be addressed with the patient separately from the product specific information.
5. The "What is the most important information I should know about ILARIS?" heading was removed and the information was moved to the "serious side effects" section.
6. In the "What should I tell my healthcare provider before taking ILARIS?" section we removed:
   - [redacted] b(4)
   - have tuberculosis (TB)
   - have HIV, Hepatitis B, or Hepatitis C

   These are not listed in the PI. For consistency if the Applicant wishes to add these to the PPI they must first be added to the PI.
7. In the "What should I tell my healthcare provider before taking section [redacted] was removed because it is not listed in the PI. For consistency if the Applicant wishes to add this to the PPI it must first be added to the PI.
8. In the "How should I take?" section all information about [redacted] of ILARIS has been removed, [redacted] b(4)
9. The "How should I store ILARIS?" section was removed because this will be given by a healthcare provider and not stored by the patient.
10. After the "General Information about the safe and effective use of ILARIS" section the Applicant should add a contact phone number.

Please let us know if you have any questions.

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X_ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Department of Health and Human Services
Public Health Service
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Office of Surveillance and Epidemiology

Date:	May 11, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Through:	Claudia Karwoski, Pharm.D., Director (Acting) 5/11/09 Division of Risk Management (DRISK)
From:	**OSE Ilaris Review Team** Scientific Lead: Kendra Worthy, Pharm.D., Drug Risk Management Analyst (DRISK) Team Members: Mary Dempsey, Risk Management Program Coordinator (DRISK) Kathy O'Connell, M.D., Ph.D., Medical Officer (DRISK) Christopher Wheeler, Pharm.D., Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Subject:	Review of Risk Management Plan
Drug Name(s):	Ilaris® (canakinumab)
Application Type/Number:	BLA 125319
Applicant/sponsor:	Novartis
OSE RCM #:	2009-63

CONTENTS

1 INTRODUCTION

This review follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed "Safety Risk Management Plan" for Ilaris (canakinumab) received on December 15, 2008.

Ilaris (canakinumab) is an interleukin-1 antagonist administered by subcutaneous injection for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children aged 4 years and older. The syndromes include:

- Familial Cold Autoinflammatory Syndrome (FCAS)/Familial Cold urticaria (FCU),
- Muckle-Wells Syndrome (MWS), and
- ——— b(4)

The 150mg/mL injection is dosed at 150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight between 15 kg and 40 kg; the single subcutaneous injection is administered every 8 weeks.

The BLA for Ilaris was granted orphan status on December 18, 2007 and priority review status on June 27, 2008. Orphan designation has also been granted for the European Union application.

2 MATERIAL REVIEWED

The following documents were reviewed –

- Safety Risk Management Plan, received December 15, 2008, for Ilaris, available in EDR;
- Ilaris proposed package insert, document received December 15, 2008, available in EDR;
- Novartis media release dated November 19, 2008 http://www.novartis.com/newsroom/media-releases/en/2008/1271207.shtml;
- Orphan designation letter dated December 18, 2007;
- FDA Filing Communication stating priority status dated February 13, 2009.
- OSE Review of Rilonacept Risk Management Plan, review completed October 29, 2007; available in DFS

3 RESULTS OF REVIEW

3.1 APPLICANT'S SAFETY CONCERNS

Efficacy, safety, and tolerability data on Ilaris from CAPS studies were completed with 78 subjects; 15 of those being children. Safety data are provided from the results of three clinical trials: a placebo-controlled long-term efficacy trial, a dose-finding trial, and an uncontrolled long-term safety and efficacy trial in CAPS. Several patients moved across trials and contributed data to more than one trial.

Novartis reports infections as an important identified risk. Of the 95 reported infections in CAPS patients, two were considered serious. Both cases were attributed to treatment with Ilaris, and both patients fully recovered. No cases were fatal.

Novartis acknowledges the following as potential risks for further evaluation:

- Severe injection site reaction
  - No adverse events of severe injection site reactions were reported in CAPS patients; however, injection site reactions are a known tolerability issue with other biologics.
- Immunogenicity
  - There were no signs or reports of immunogenicity or allergenicity during preclinical trials in marmoset or in clinical trials with CAPS patients; however, a potential risk remains: Ilaris is a recombinant protein derived from a genetically engineered mouse that carries part of human IgG.
- Opportunistic infections
  - No infections have been reported in CAPS patients studied. Interleukin-1 is a pro-inflammatory cytokine that enhances the immune response; inhibition could potentially have an effect on immune response.
- Malignancy
  - No malignancy cases in CAPS patients have been reported. The sponsor states this risk is unknown; however, IL-1 antagonism potentially causes immunosuppression thereby increasing the risk of tumors.
- Lymphoid organ toxicity
  - Lymphoid hyperplasia was seen in male marmosets during one pre-clinical study which could not be reproduced in other studies. There has been no evidence in humans.
- Neutropenia
  - Three reports of neutropenia were observed during clinical trials; two of the reports were not confirmed by laboratory values recorded in the clinical trial database.
- Vertigo
  - Ten out of 78 patients (13%) reported vertigo; two as a serious adverse event. Seven out of 10 cases required no treatment. Symptoms were generally mild and resolved the same day. No cases led to discontinuation of the drug.
- Bilirubinemia
  - An asymptomatic and minimal elevation of total serum bilirubin was observed in one of the clinical trials. No concomitant elevation of liver enzymes was observed.
- Hypercholesterolemia
  - Abnormal lipid profiles have been observed with other interleukin antagonists; no cases of abnormalities in the lipid profile were seen in CAPS patients treated with Ilaris.

The applicant also identifies two potential interactions:

- Vaccines
  - No studies have been performed to examine the effects of live vaccination in patients receiving Ilaris, but the proposed labeling states in the Warnings and Precautions section that live vaccines should not be given with Ilaris. Patients should receive all recommended vaccinations prior to receiving Ilaris.
- Pharmacodynamic interactions
  - The proposed labeling states that use of Ilaris with TNF inhibitors is not recommended because of the increased risk of serious infections.

3.2 DAARP Safety Concerns

During the mid-cycle meeting on March 5, 2009, DAARP stated that at present, the medical officer had not found anything of significant concern to require Risk Evaluation and Mitigation Strategies (REMS). In an internal team meeting April 16, 2009, DAARP stated that there were no new safety concerns or additional serious adverse events.

3.3 OSE Safety Concerns

OSE has not identified any additional safety concerns that warrant consideration of a REMS at this time for the proposed indication.

3.4 Proposed Safety Risk Management Plan

Novartis submitted a Safety Risk Management Plan in the European Union format that proposed labeling, routine pharmacovigilance, and a registry study to further assess and manage the risks with Ilaris. The purpose of the registry is to monitor long-term safety and clinical data and patient reported outcomes to further establish the safety profile of Ilaris in the post-marketing setting.

4 DISCUSSION AND CONCLUSION

DAARP does not feel that additional measures beyond labeling and routine pharmacovigilance are needed for Ilaris. DRISK agrees that the proposed routine approach is sufficient to address the identified risk of infection and other potential risks at this time. Should DAARP raise further concerns about risks outlined above or identify additional risks associated with Ilaris warranting more extensive risk mitigation or elements of a REMS including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use do not appear to be warranted, please send a consult to OSE Division of Risk Management. Please consult with the Division of Epidemiology if you would believe the registry study that the company proposes should be a post-marketing requirement (PMR).