CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319Orig1s085, 086, 087

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	sBLA 125319/085, 086, 087
Product Name:	Ilaris (canukinumab)
PMR/PMC Description:	Submit data from the randomized withdrawal period (Epoch 3) of the ongoing phase 3 study, CACZ885N2301 (N2301). Include in the study report an assessment of the maintenance of efficacy of canakinumab at a reduced dosing frequency.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	10/31/2016
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

It is appropriate for randomized withdrawal data to be assessed as a PMC/PMR instead of pre-approval because the safety and efficacy of canakinumab for Familial Mediterranean Fever (FMF), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), and Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) has been established pre-approval. These are rare, serious diseases with unmet need. According to the sponsor's study report, the following subjects (randomized canakinumab responders in Epoch 2) are eligible for Epoch 3: (b) (4)

We feel that this limited number of subjects on a medication with an established safety profile, enrolled in a pivotal study of an agent for which breakthrough therapy designation has been granted merits a PMC as opposed to a pre-approval requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This PMC is requested in order to obtain the data from Epoch 3, the ongoing, 24-week randomized withdrawal epoch of the sponsor's single pivotal Phase 3 study, CACZ885N2301, during which responders to canakinumab are re-randomized to canakinumab 150 mg every 8 weeks or placebo to assess the potential for canakinumab to maintain clinical efficacy at a reduced dosing frequency. (b) (5) [redacted] In the current BLA, the sponsor submitted data from Epoch 2 of the study, which has a randomized, double-blind, placebo controlled design. Patients with FMF, HIDS/MKD, and TRAPS were randomized to 150 mg canakinumab or placebo once every 4 weeks. Patients with ongoing disease activity either initiated 150 mg canakinumab (if on placebo) or increased their dose to 300 mg (if on 150 mg canakinumab). This Epoch clearly demonstrated efficacy of canakinumab compared to placebo. However, there are limitations to the interpretation of the data given the cross-over between study arms and the dose escalation. The requested PMC data will evaluate if efficacy can be maintained at a reduced dosing frequency. This will help inform the optimal use of the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMC is requested obtain the data from the randomized withdrawal period (Epoch 3) of the ongoing phase 3 study, CACZ885N2301.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

  This PMC is requested to obtain the data from Epoch 3, the ongoing, 24-week randomized withdrawal epoch of the sponsor's single pivotal Phase 3 study, N2301, during which responders to canakinumab are re-randomized to canakinumab 150 mg every 8 weeks or placebo to assess the potential for canakinumab to maintain clinical efficacy at a reduced dosing frequency. (b) (5)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   - ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   - ☒ Are the objectives clear from the description of the PMR/PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
09/19/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 14, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125319/S-85,86,87 BLA 125319/S-88
Product Name and Strength:	Ilaris (canakinumab) For Injection 150 mg per vial , 150 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis
Submission Dates:	BLA 125319/S-88: March 30, 2016, July 25, 2016, July 28, 2016, and August 23, 2016 BLA 125319/S-85: March 23, 2016 and August 12, 2016 BLA 125319/S-86: March 28, 2016 BLA 125319/S-87: March 29, 2016
OSE RCM #:	2016-1705 and 2016-1125
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

BLA 125319/Supplement-088: This review evaluates the proposed Prescribing Information (PI), carton labeling, and container labels for BLA 125319/S-088, Ilaris (canakinumab), submitted on March 30, 2016 and July 25, 2016. The Applicant submitted a Labeling Prior Approval Supplement (PAS) which proposes an additional dosage form of Ilaris 150 mg/mL solution in a single-dose vial. Additionally, the supplement proposes revised labels and labeling for the 150 mg per vial solution for injection in order to clarify for healthcare providers that the reconstituted product is a 150 mg/mL solution. This supplement received a Complete Response on July 29, 2016 due to product quality deficiencies. The Applicant re-submitted BLA 125319/S-088 on August 23, 2016.

BLA 125319/Supplement-085, 086, 087: This review also evaluated the Prescribing Information (PI), carton labeling, and container labels for BLA 125319/ S-085, S-086, and S-087 Ilaris (canakinumab), submitted on March 23, 2016, March 28, 2016, March 29, 2016 and August 12, 2016. The applicant submitted Labeling Efficacy Prior Approval Supplement (PAS) which proposes the following indications: Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older (S-085), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) in adults and children 2 years of age and older (S-086), and 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 (S-087).

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) requested that we review the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 SUPPLEMENT 88

Proposed Injection vial:

Novartis is proposing to add a new dosage form of Ilaris 150 mg/mL solution in single-dose vials. The product is currently available as a lyophilized powder, containing 180 mg of canakinumab, in a single-dose vial for reconstitution. Each vial is to be reconstituted with 1 mL of Sterile Water for Injection to result in a 150 mg/mL solution for subcutaneous injection. DMEPA evaluated the introduction of this new dosage form to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the strength (150 mg/mL) of the proposed dosage form will be inconsistent with the strength (180 mg) of the current lyophilized powder dosage form. However, the Applicant also proposes to revise the strength of the current dosage form to 150 mg/vial (see Lyophilized powder vial section below). DMEPA finds that the proposed dosage form of 150 mg/mL solution supports the dosage and administration for this product and thus finds the Applicant's proposal acceptable.

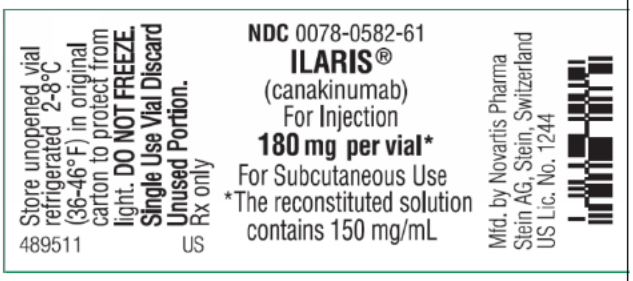
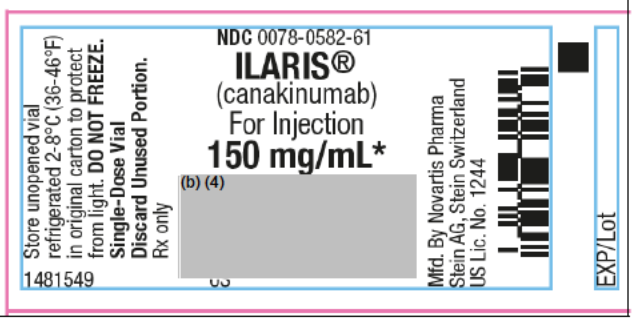
Lyophilized powder vial:

The currently approved lyophilized powder vial is currently labeled as 180 mg per vial. Following reconstitution with 1 mL of Sterile Water for Injection, only 150 mg can be extracted from the vial. Therefore, the currently approved labels do not reflect the extractable volume.

The Applicant states that they have received numerous inquiries relating to the lyophilized powder presentation (see Appendix F for more details). Specifically, in their report, Novartis identified and evaluated 21 medication error reports related to dosing errors, categorized as follows:

- Incorrect dose (n=14),
- Medication error (n=6),
- Drug administration (n=1).

These errors were determined to occur as a result of dose calculation errors (n=12) or no cause could be determined or no information provided (n=9). No outcomes were reported. With regard to the dose calculations errors, the Applicant reports that these errors may be potentially attributed to healthcare providers' confusion that the 1 mL solution after reconstitution contains 180 mg of canakinumab, rather than the total concentration of 150 mg/mL. According to their analysis, the Applicant cites the labels and labeling as a potential cause of these errors, as the current labels and labeling prominently states the strength of "180 mg per vial" but less prominently states that after reconstitution, 1 mL can be withdrawn from the vial (which contains only 150 mg of canakinumab). However, the Applicant's report does not provide a root cause analysis as reported in the cases. The current container label and proposed container label (submitted on March 30, 2016) are shown below:

Current Container Label (per August 12, 2015 Annual Report)	Proposed container label (submitted on March 30, 2016)
	

As a result of these reports, the Applicant proposes to revise the currently approved Ilaris labels and labeling to state the final concentration after reconstitution, which is 150 mg/mL, instead of the total amount of drug per vial of 180 mg. Additionally, Novartis proposes to revise the Prescribing Information (Sections 2 Dosage and Administration, 3 Dosage Forms and Strengths, 11 Description, and 16 How Supplied/Storage and Handling) to further clarify the final concentration after reconstitution.

DMEPA also searched for medication errors associated with the currently marketed Ilaris. Our search identified 392 U.S. suspected medication error cases. The cases are summarized in Appendix E.

Our search identified 94 cases of wrong dose medication errors of which 21 of these cases were the same as identified by Novartis. In the majority of the wrong dose medication error cases, no root cause or outcome was reported (n=85) and the errors occurred amongst a range of doses (within the dosing range for Ilaris [n=70], overdose [n=13], underdose [n=2]).

Although most of the cases did not provide a root cause, we compared the intended dose and the dose that was administered. We note that in 11 of these cases, this error could be attributed to users assuming that the final concentration of Ilaris is 180 mg/1. 2 mL. In these 11 cases, the intended dose was 150 mg, however the actual dose users received was based on calculations that assumed the final concentration of Ilaris is 180 mg/1.2 mL.

In addition, we evaluated the DOSAGE AND ADMINISTRATION section in the Prescribing Information as well as the container labels and carton labeling and do not have any additional recommendations at this time. The DOSAGE AND ADMINISTRATION section clearly states the indications, recommended frequency, and it provides detailed preparation and administration instructions. In addition, the HOW SUPPLIED/STORAGE AND HANDLING section in the PI provides detailed storage instructions. The carton labeling provides storage requirements and refers users to the Prescribing Information for dosage, dilution, and administration information. The container label provides the storage requirement and states to "reconstitute prior to use".

In the evaluation of the Applicant's proposal to revise the strength statement of the lyophilized powder for injection dosage form, DMEPA consulted with the Office of Biological Products (OBP). Per OBP, the strength presentation on the labels and labeling is dependent on the extractable volume data per FDA guidance "*Allowable Excess Volume and Labeled Vial Fill Size*

in Injectable Drug and Biological Products - Guidance for Industry" (June 2015). According to the Applicant's response to an Information Request, submitted on July 25, 2016, results of the extractable volume study support that 1 mL of reconstituted solution can be withdrawn from the vial. Therefore, DMEPA/OBP recommend that the Applicant revise the strength statement from their proposal of "150 mg/mL*" to "150 mg/vial". We also recommend removing the statement (b) (4) as this may create additional confusion for healthcare providers.

In order to educate health care providers on the labeling change regarding the strength statement, we recommend that Novartis provide a communication plan in order to mitigate the potential for wrong dose errors due to confusion by those healthcare providers who are familiar with the current product and how the strength is labeled. (b) (4) .

DMEPA reviewed the proposed labels and labeling submitted on March 30, 2016. Recommendations to increase readability and prominence of important information to promote the safe use of the product were communicated to the Applicant on July 19, 2016 and July 27, 2016 from OBP, for which DMEPA concurred (See Appendix F for more details).[1] As Supplement-088 received a Complete Response on July 29, 2016 due to product quality deficiencies, the revised container label and carton labeling for the lyophilized powder formulation was submitted to Supplement-085 on August 12, 2016. DMEPA finds the Applicant's proposal, prescribing information, container labels, and carton labels submitted on August 12, 2016 acceptable from a medication errors perspective.

3.2 SUPPLEMENTS 85, 86, AND 87

The applicant submitted Labeling efficacy supplements for the following proposed indications: Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older, Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) in adults and children 2 years of age and older, and 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.

DMEPA evaluated the dosage and administration of the proposed indications (see appendix A) to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. DMEPA finds that the dosage and administration for the proposed indications is supported by the currently approved dosage form and strength for this product and thus, we find the Applicant's proposal acceptable. In addition, we performed a risk assessment of the proposed container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors. We find the labels and labeling acceptable from a medication error perspective.

[1] DARRTs submission dated July 19, 2016: sBLA 125319/S-088 Labeling Comments. Revised labels and labeling submitted by Novartis on July 25, 2016 (Supporting Document Number 581; eCTD Sequence Number 0236). DARRTs submission dated July 27, 2016: sBLA 125319/S-088 Labeling Comments. Revised labels and labeling submitted via email in advance of the official submission by Novartis on July 28, 2016.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the container labels and carton labeling submitted on July 28, 2016 and August 12, 2016 acceptable and do not have any recommendations at this time. In addition, we also find the Prescribing Information acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ilaris that Novartis submitted on March 30, 2016 and July 25, 2016.

Table 2. Relevant Product Information for Ilaris	
Initial Approval Date	2009
Active Ingredient	canakinumab
Indication	**Cryopyrin-Associated Periodic Syndromes (CAPS)**, in adults and children 4 years of age and older including: • Familial Cold Autoinflammatory Syndrome (FCAS) • Muckle-Wells Syndrome (MWS) **Active Systemic Juvenile Idiopathic Arthritis (SJIA)** in patients aged 2 years and older
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	180 mg
Dose and Frequency	• **Cryopyrin-Associated Periodic Syndromes (CAPS):** 150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Administer subcutaneously every 8 weeks. (2.2) • **Systemic Juvenile Idiopathic Arthritis (SJIA):** 4 mg/kg (with a maximum of 300 mg) for patients with a body weight greater than or equal to 7.5 kg. Administer subcutaneously every 4 weeks. (2.3)
How Supplied	Sterile, single-use, glass vial containing 180 mg of ILARIS as a lyophilized powder for reconstitution
Storage	Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F). Do not freeze. Store in the original container to protected from light.
Proposed Additions	• 150 mg/mL solution in single-dose vials • 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.

	• 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 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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 26, 2016, we searched the L:drive and AIMS using the terms, Ilaris and canakinumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[2,3]that was relevant to this and we confirmed that our previous recommendations were implemented.

[2] McMillan T. Label and Labeling Review for Ilaris (BLA 125319). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 MAR 12. RCM No. 2013-258.

[3] McMillan T. Label and Labeling Review for Ilaris (BLA 125319). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 1. RCM No. 2015-2369.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on July 27, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[4]

Table 3: FAERS Search Strategy

Date Range	**January 31, 2013-July 26, 2016**
Product	Canakinumab [active ingredient] Ilaris [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

[4] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

E.2 Results

Our search identified the following 394 wrong dose medication error cases for this review:

Summary of U.S. Suspected Ilaris Medication Error Cases in FAERS, (January 31, 2013 to July 26, 2016)		
Type of Medication Error or Event	**# of U.S. Cases**	**DMEPA Reviewer Comment**
Wrong Frequency	269	• Every 28 days, 10 weeks, 11 weeks, 12 weeks or was late due to insurance issues. No root cause or outcomes were reported
Wrong dose	94	• No root cause or outcome was reported (n=85) and the errors occurred amongst a range of doses (within the dosing range for Ilaris [n=70], overdose [n=13], underdose [n=2]). • The following nine cases reported the root causes: wrong dose on pharmacy label (n=4), the physician wrote the wrong order (n=2), the nurse incorrectly calculated the dose and therefore administered the incorrect dose (n=1), the nurse only had one vial and therefore administered the wrong dose (n=-1), and the white part of the needle came off and the nurse could not administer the correct dose (n=1).
Dose omission	10	• Not related to medication errors (e.g. insurance coverage lapse, skipped dose because of illness or side effects, or no reason given)
Other	7	• Unlabeled age limit • Duplicate • Medication error unrelated to Ilaris
Incorrect drug administration/wrong technique	5	• Not applying enough pressure to give injection • Needle came apart while receiving injection • Mixed incorrectly- added more sterile water than needed due to the inability to mix completely or did not add sterile water
Wrong Indication	4	• Ilaris was prescribed and administered for the following off-labeled indications: Rheumatoid Arthritis, Still's disease, Psoriatic Arthroplasty, and Immunodeficiency.
Wrong Storage	3	• Shipped without ice packs or left unrefrigerated

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the 94 cases of wrong dose medication error relevant for this review.

11704151	11603325	11825961	12051321	12321041	12467492	12578553
11239512	11614344	11829692	12067288	12327401	12469388	12578563
11431012	11615084	11837152	12078652	12328096	12469407	12580689
11229809	11658754	11851880	12085248	12329330	12469409	12592245
11285702	11688276	11868284	12096254	12329391	12476530	
11307689	11702210	11868606	12134051	12334876	12482703	
11463108	11703617	11871477	12152934	12355058	12486575	
11463245	11703945	11873883	12165655	12366126	12486726	
11464628	11748385	11876933	12247209	12367502	12518954	
11464643	11771192	11885413	12248317	12369303	12529361	
11518558	11774496	11924967	12268320	12370735	12539198	
11527233	11779615	11925148	12268408	12413521	12540781	
11527331	11781028	11925463	12271320	12443185	12546652	
11527367	11792992	11990612	12271847	12449070	12551803	
11527837	11796095	12014879	12272252	12452857	12565933	

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX F. OTHER

Medication Error Reports submitted by Novartis on March 30, 2016

Ilaris_Med Errors due to Dosing Issues.pdf

OBP/DMEPA Container Label and Carton Labeling Recommendations communicated to Applicant on July 19, 2016:

A. General Comments (solution and lyophilized powder products)

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.

2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

B. Carton Labeling for Solution Vial

1. Relocate the dosage form to appear under the non-proprietary name. This is the appropriate presentation for CDER specified biologics.

2. Add the route of administration to appear after the strength on the side panels.

3. Add "Single-Dose Vial. Discard Unused portion" to appear under the route of administration on the PDP.

4. Delete "(b) (4) " or decrease the prominence and relocate it to the upper right portion of the PDP near the Rx only statement.

5. Revise the manufacturer information so that the licensed manufacturer name, address, and license number are listed as "Manufactured by" to comply with 21 CFR 610.61(b). For example:

   Manufactured by:

   Novartis Pharmaceuticals Corporation

   East Hanover, NJ 07936

   US License No. 1244

If you wish to include the drug product facility, you may label as:

at:

Novartis Pharma Stein AG

Stein, Switzerland

The distributor name and address can appear as proposed provided that you list the licensed manufacturer as described above per 21 CFR 610.64. This presentation is similar to your Cosentyx (secukinumab) and Arzerra (ofatumumab) products.

6. Revise the list of ingredients on the back panel to appear in alphabetical order to comply with USP <1091 > Labeling of Inactive Ingredients.

C. Container Label for Solution Vial

1. Currently the license number assigned to Novartis Pharmaceuticals Corporation appears to be assigned to Novartis Pharma of Switzerland. Revise the manufacturer information so that the licensed manufacturer name, address, and license number are listed as "Manufactured by" to comply with 21 CFR 610.60(a)(2). For example:

   Mfd by Novartis Pharmaceuticals Corporation
   East Hanover, NJ 07936
   US License No. 1244

2. Considering this is a partial label per 21 610.60(c), may list only the required licensed manufacturer name "Mfd by Novartis Pharmaceuticals Corporation".

D. Carton Labeling for Lyophilized Powder Vial

1. Revise the dosage form "for Injection" to similar font style as the non-proprietary name.

2. Add the dosage form "for Injection" to appear under the non-proprietary name on the side panels.

3. Provide the extractable volume data and revise the strength presentation based on this data. For example:

   a. If the extractable volume data supports 1 mL of reconstituted solution can be withdrawn from the vial, then revise the strength presentation from "150 mg/mL*" to "150 mg/vial".

   b. If the extractable volume data supports 1.2 mL of reconstituted solution can be withdrawn from the vial, then revise the strength presentation from "150 mg/mL*" to "180 vial".

c. Delete (b) (4) from the PDP.

4. Add the statement “Reconstitute Prior to Use” on the PDP below the route of administration.

5. Revise “Single-dose vial” on the PDP to read “Single-Dose Vial. Discard Unused Portion.”

6. Revise the list of ingredients of the reconstitution instructions on the PDP to appear in alphabetical order to comply with USP <1091 > Labeling of Inactive Ingredients. For example:

> Reconstitute with 1 mL of preservative-free Sterile Water for Injection to obtain a concentration of 150 mg/mL canakinumab, polysorbate (0.6 mg/mL), L-histidine (x mg/mL), L-histidine hydrochloride monohydrate (x mg/mL), and sucrose (92.38 mg/mL).

Additionally:

a. Note deletion of the trailing zero (0.60 mg/mL to 0.6 mg/mL).

b. Clarify if preservative-free Sterile Water for Injection is required for reconstitution. The PI and carton labeling are inconsistent with the use of “preservative-free Sterile Water for Injection”, ”Sterile Water of Injection”, and “water for injection”.

c. Clarify the amounts of L-histidine and L-histidine hydrochloride monohydrate.

d. Ensure the listing of inactive ingredients and amounts are consistent with section 11 - DESCRIPTION in the PI.

7. See B.5.

E. Container Label for Lyophilized Powder Vial

1. See comment D3.

2. Add the statement “Reconstitute Prior to Use” on the right-side of the label above the manufacturing information.

3. Revise the manufacturer information so that the licensed manufacturer name appears on the label to create space for the above comment. Considering this is a partial label per 21 610.60(c), you may list only the required licensed manufacturer name: “Mfd by”. For example:

> Mfd by Novartis or Novartis Pharmaceuticals Corporation

OBP/DMEPA Container Label and Carton Labeling Recommendations communicated to Applicant on July 27, 2016:

A. General Comments

1. (b) (4) communication plan to educate healthcare practitioners on the lyophilized powder vial labeling change.

B. Carton Labeling for Lyophilized Powder Vial

7. Revise the dosage form "For Injection" to read "for Injection" to be consistent with the presentation in USP General Chapters: <1> Injections, Nomenclature and Definitions.

8. Add the strength and route of administration under the name and dosage form on the on the side panels similar to the presentation on the solution vial.

Ilaris

(canakinumab)

for Injection

150 mg/vial

For Subcutaneous Use

C. Container Label for Lyophilized Powder Vial

1. See B1.

2. Bold "Reconstitute Prior to Use" to increase the prominence.

(b) (4)

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/s/

TERESA S MCMILLAN
09/14/2016

MISHALE P MISTRY
09/14/2016

LUBNA A MERCHANT
09/14/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 12, 2016

To: Brandi Wheeler, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Taylor Burnett, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Trung-Hieu Brian Tran, Pharm.D., MBA
Regulatory Review Officer
OPDP

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: BLA 125319/S-85, 86, 87
OPDP labeling comments for ILARIS® (canakinumab) for injection, for subcutaneous use (Ilaris)

OPDP has reviewed the revised proposed Package Insert (PI) and Medication Guide (MG) for Ilaris submitted for consult on May 17, 2016.

OPDP acknowledges that this is an efficacy supplement for an approved product; however, some of our comments included within this review apply to existing sections of the labeling that are already approved.

OPDP's comments on the PI and MG are based on the proposed draft marked-up labeling titled "Ilaris08_30_16proposed-.doc" that was sent via email from DPARP to OPDP on August 30, 2016. OPDP's comments on the PI and MG are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions concerning the PI or MG, please contact Taylor Burnett at (240) 402-1349 or taylor.burnett@fda.hhs.gov.

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/s/

TAYLOR B BURNETT
09/12/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 31, 2016
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ILARIS (canakinumab)
Dosage Form and Route:	Injection for Subcutaneous Use
Application Type/Number:	BLA 125319
Supplement Number:	S-085, S-086, S-087
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On March 23, 2016, Novartis Pharmaceutical Corporation submitted for the Agency's review a Supplemental Biologics License Application (sBLA-083) for ILARIS (canakinumab) injection for subcutaneous use. The purpose of this submission is to seek marketing approval for the treatment of Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older.

Subsequently, on March 28, 2016 the Applicant submitted a Supplemental Biologics License Application (sBLA-085) for ILARIS (canakinumab) injection for subcutaneous use, seeking marketing approval for the treatment of Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) in adults and children 2 years of age and older.

On March 29, 2016, the Applicant submitted a Supplemental Biologics License Application (sBLA-086) for ILARIS (canakinumab) injection for subcutaneous use, seeking marketing approval for the treatment of Familial Mediterranean Fever (FMF) in adults and children 2 years and older in whom cholchicine is contraindicated, is not tolerated or does not provide adequate response.

ILARIS (canakinumab) was originally approved on June 17, 2009 and is currently indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome, in adults and children 4 years of age and older and for treatment of Systemic Juvenile Idiopathic Arthritis in patients aged 2 years and older.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on May 17, 2016 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for ILARIS (canakinumab) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ILARIS (canakinumab) injection for subcutaneous use, MG received on March 23, 2016 (S-085), March 28, 2016 (S-086), and March 29, 2016 (S-087) and received by DMPP on September 30, 2016.
- Draft ILARIS (canakinumab) injection for subcutaneous use, Prescribing Information (PI) received on March 23, 2016 (S-085), March 28, 2016 (S-086), and March 29, 2016 (S-087), revised by the Review Division throughout the review cycle, and received by DMPP on September 30, 2016.
- Approved ILARIS (canakinumab) injection for subcutaneous use labeling dated July 21, 2016

3 REVIEW METHODS

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
08/31/2016

LASHAWN M GRIFFITHS
08/31/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125319/S-085, 086, 087

Application Type: Efficacy Supplement

Drug Name(s)/Dosage Form(s): Ilaris (canakinumab) injection

Applicant: Novartis

Receipt Date: March 23, 28, and 29, 2016

Goal Date: September 23, 28, and 29 2016

1. Regulatory History and Applicant's Main Proposals

Novartis submitted three efficacy supplements for Ilaris (canakinumab) to include indications of TRAPS, HIDS and FMF on March 23, 28, and 29, 2016.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *We will add waiver language to approval letter.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

BRANDI E WHEELER
08/26/2016

LADAN JAFARI
08/26/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125319	NDA Supplement #: S- BLA Supplement #: S- 85,86,87	Efficacy Supplement Category: ☒ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Ilaris Established/Proper Name: Canakinumab Dosage Form: Injection Strengths: 150 mg/ml		
Applicant: Novartis Pharmaceutical Corporation Agent for Applicant (if applicable):		
Date of Application: S-85 March 23, 2016, S-86 March 28, 2016, S-87 March 29, 2016 Date of Receipt: S-85 March 23, 2016, S-86 March 28, 2016, S-87 March 29, 2016 Date clock started after UN:		
PDUFA Goal Date: S-85 September 23, 2016, S-86 September 28, 2016 S-87 September 29, 2016	Action Goal Date (if different): September 23, 2016	
Filing Date: May 22, 2016	Date of Filing Meeting: May 3, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Addition of TRAPS, HIDS/MKD, FMF		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 100040	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☐		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.*
Forms *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uc

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

m027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☐	☐ ☐	☐ ☐	PLLR format conversion in supplement 84, PDUFA goal date 07/22/16
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☒	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 05/13/2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/02/2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 3, 2016

BACKGROUND: Novartis submitted three efficacy supplements on March 23, 28, and 29, 2016 for the indications of TRAPS, HIDS, and FMF. The Division has decided to review the supplements together with a goal date of September 23, 2016

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brandi Wheeler	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Janet Maynard		Y
Division Director/Deputy	Badrul Chowdhury		Y
Office Director/Deputy			
Clinical	Reviewer:	Mark Borigini	Y
	TL:	Janet Maynard	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jianmeng Chen	Y
	TL:	Anshu Marathe	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Lan Zeng	Y

	TL:	Greg Levin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tim Robison	Y
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Rashmi Rawat	Y
	RBPM:	Andrew Shiber	N
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:	Chikako Torigoe	N
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul Chowdhury **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRANDI E WHEELER
05/19/2016

LADAN JAFARI
05/19/2016