CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212035Orig1s000

OTHER REVIEW(S)

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:	April 23, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 212035
Product Name and Strength:	Argatroban in 0.9% Sodium Chloride Injection 50 mg/50mL (1 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord Healthcare Inc. (Accord)
FDA Received Date:	April 7, 2021
OSE RCM #:	2018-896-4
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Accord submitted a Class 1 resubmission for NDA 212035 for Argatroban in 0.9% Sodium Chloride Injection on April 7, 2021 to request final approval of the application. DMEPA reviewed the proposed container label, carton labeling, and Prescribing Information for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On April 30, 2018, Accord submitted NDA 212035 for Argatroban in 0.9% Sodium Chloride Injection. DMEPA completed a label and labeling review on October 12, 2018, and subsequent label and labeling review memos on December 4, 2018, February 13, 2019, and February 26, 2019 (see Appendix B). On February 28, 2019, Accord received a Tentative Approval letter for Argatroban in 0.9% Sodium Chloride Injection "for use as recommended in the agreed-upon labeling (text for the Prescribing Information) and submitted labeling (carton and container labeling submitted February 22, 2019)". The application was not eligible for approval at that time due to the Sponsor's "failure to comply with the statutory requirements for the timing of sending notice of paragraph IV certification as set forth in section 505(b)(3)(B) of the Federal Food, Drug, and Cosmetic Act".

1.2 PRODUCT BACKGROUND

Argatroban is marketed by various manufacturers as 250 mg/2.5 mL, 125 mg/125 mL, and 50 mg/50 mL in single-dose vials. The Sponsor noted in their original submission that the proposed product, Argatroban in 0.9% Sodium Chloride Injection, 50 mg/50 mL, is identical to Reference Listed Drug (RLD) Argatroban in sodium chloride injection, [redacted] (b) (4) in terms of route of administration, dosage form, concentration, and indications.

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 – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Accord submitted a Class 1 resubmission for NDA 212035 for Argatroban in 0.9% Sodium Chloride Injection to request final approval of the application. We performed a risk assessment of the proposed labels and labeling to identify areas of vulnerability with regards to medication errors.

We note the proposed Prescribing Information, contain label, and carton labeling are the same as the previously agreed upon labeling, and as such, we have no recommendations at this time.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes the proposed Prescribing Information, container label, and carton labeling are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Argatroban in 0.9% Sodium Chloride Injection submitted by Accord on April 7, 2021 and the reference listed drug (RLD)[a].

Table 2. Relevant Product Information for Argatroban and the Listed Drug		
Product Name	Argatroban in 0.9% Sodium Chloride Injection	Argatroban in Sodium Chloride Injection
Initial Approval Date	Tentative approval: 02/28/2019	(b) (4)
Active Ingredient	argatroban	argatroban
Indication	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Route of Administration	Intravenous infusion	Intravenous infusion
Dosage Form	Injection	Injection
Strength	50 mg/50 mL (1 mg/mL)	(b) (4) (1 mg/mL)
Dose and Frequency	• Argatroban 50 mg in 50 mL aqueous sodium chloride solution (1 mg/mL) is intended for administration to adult patients • Discontinue all parenteral anticoagulants before administering Argatroban • Adjust dosing in patients with HIT who have moderate or severe hepatic impairment <u>Heparin-Induced Thrombocytopenia</u> The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min	• Argatroban (b) (4) aqueous sodium chloride solution (1 mg/mL) is intended for administration to adult patients • Discontinue all parenteral anticoagulants before administering Argatroban • Adjust dosing in patients with HIT who have moderate or severe hepatic impairment <u>Heparin-Induced Thrombocytopenia</u> The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min

[a] Argatroban Injection. NDA 022485. Prescribing Information. Excerpted from Drugs at FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022485s013lbl.pdf

	administered as a continuous infusion • Discontinue heparin therapy and obtain a baseline aPTT before administering Argatroban • After the initial dose of Argatroban, the dose can be adjusted as clinically indicated <u>Percutaneous Coronary Intervention</u> The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes • Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds • Monitoring therapy and dosage adjustments recommendations should be followed • See special dosing recommendations for hepatic and renal impaired patients	administered a s a continuous infusion • Discontinue heparin therapy and obtain a baseline aPTT before administering Argatroban • After the initial dose of Argatroban, the dose can be adjusted as clinically indicated <u>Percutaneous Coronary Intervention</u> The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes • Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds • Monitoring therapy and dosage adjustments recommendations should be followed • See special dosing recommendations for hepatic and renal impaired patients
How Supplied	Argatroban in Sodium Chloride Injection is supplied as a single dose vial containing 50 mg argatroban in 50 mL of aqueous sodium chloride solution (1 mg/mL). The vial is sealed with a gray rubber stopper and a green aluminum flip-off seal. • NDC 16729-430-11 – Package containing one vial of Argatroban Injection in 0.9% Sodium Chloride (each vial contains 50 mg of argatroban). • NDC 16729-430-43 – Package containing 10 vials of Argatroban	Argatroban Injection is supplied as a single use vial containing (b) (4) argatroban in (b) (4) aqueous sodium chloride solution (1 mg/mL). (b) (4)

	Injection in 0.9% Sodium Chloride (each vial contains 50 mg of argatroban).	
Storage	Store vials in their original carton at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] to protect from light. DO NOT FREEZE.	Store the vials in original cartons at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light. (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 20, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "argatroban" and "NDA 212035". Our search identified 4 previous labeling reviews and we confirmed that our previous recommendations were implemented.

Reviewer	Document Title	Application	Date	RCM No.
Ogbonna, C.	Label and Labeling Review Memo for Argatroban	NDA 212035	2019 FEB 26	2018-896-03
Ogbonna, C.	Label and Labeling Review Memo for Argatroban	NDA 212035	2019 FEB 13	2018-896-02
Ogbonna, C.	Label and Labeling Review Memo for Argatroban	NDA 212035	2018 DEC 04	2018-896-01
Ogbonna, C.	Label and Labeling Review for Argatroban	NDA 212035	2018 OCT 12	2018-896

APPENDIX G. LABELS AND LABELING

G.1 Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with post-market medication error data, we reviewed the following Argatroban in 0.9% Sodium Chloride Injection labels and labeling submitted by Accord Healthcare Inc. on April 7, 2021.

- Container Label
- Carton Labeling
- Prescribing Information (image not shown)
  \\CDSESUB1\evsprod\nda212035\0012\m1\us\final-labeling-text-word-0012.docx

G.2 Label and Labeling Images

Container Label

(b) (4)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

STEPHANIE L DEGRAW
04/23/2021 04:50:46 PM

HINA S MEHTA
04/28/2021 11:01:03 AM

Division of Hematology Products (DNH) Labeling Supplement Review

NDA/BLA Number	NDA 212035
Applicant	Accord Healthcare
Proprietary Name **(nonproprietary name)**	Argatroban in Sodium Chloride Injection
Receipt Date	04/07/2021
PDUFA Goal Date	06/07/2021
Review Classification	Class 1 Resubmission
Purpose of Supplement	To convert from tentative approval to regular approval.
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DNH**

Background of Application:

Labeling History

The Applicant has submitted a Class 1 Resubmission Request for Final Approval. Accord Healthcare received tentative approval for NDA 212035, Argatroban in 0.9% Sodium Chloride Injection on 02/28/2019. The reference listed drug is NDA 22434 by Eagle Pharmaceuticals.

Documents Reviewed

Sequence 0012 (SD 14)

Module 1: Administrative Information and Prescribing Information

- 1.1 Forms, Form FDA 356h
- 1.2 Cover Letter
- 1.14 Labeling
    - 1.14.2 Final Labeling
    - 1.14.3 Listed Drug Labeling

Review: I compared the most recently approved labeling for the RLD (NDA 22434) at Drugs@FDA (approved 12/06/19) to the Applicant's submitted labeling. I provided revisions to make the USPI consistent with the RLD labeling.

Summary of Labeling Recommendations:

I recommend approval of NDA 22434, Original-1 upon completion of labeling negotiations.

Attachments: USPI for NDA 22434 with my recommended edits in tracked changes with explanatory comments in bubbles.

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/s/

VIRGINIA E KWITKOWSKI
04/20/2021 12:28:46 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	February 26, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212035
Product Name and Strength:	Argatroban in 0.9% Sodium Chloride Injection, 50 mg/50 mL (1 mg/1 mL)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	February 22, 2019
OSE RCM #:	2018-896-03
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container labeling for Argatroban in 0.9% Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton and container labeling for Argatroban in 0.9% Sodium Chloride Injection are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Ogbonna C. Label and Labeling Review for Argatroban in 0.9% Sodium Chloride Injection (NDA 212035). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 13. RCM No.: 2018-896-02.

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/s/

CASMIR I OGBONNA
02/26/2019 09:51:02 AM

HINA S MEHTA
02/26/2019 12:04:31 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	February 13, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212035
Product Name and Strength:	Argatroban in 0.9% Sodium Chloride Injection, 50 mg/50 mL (1 mg/1 mL)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	February 5, 2019
OSE RCM #:	2018-896-02
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container labeling for Argatroban in 0.9% Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions were made by Accord Healthcare Inc. in their submission on February 5, 2019 to align the product title to the Prescribing Information.

2 CONCLUSION

The revised carton and container labeling is unacceptable from a medication error perspective. Per *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products* Guidance, "The concentration of the vehicle(s) named in the official title is/are stated as if part of the official title (e.g., "dextrose injection 5%," or "dextrose (5%) and sodium chloride (0.2%) injection") on the container label and carton

labeling, but not on the product title line".[a] Thus, we provide recommendations below to revise the product title on the carton and container labeling.

3 RECOMMENDATIONS FOR ACCORD HEALTHCARE INC.

We recommend the following be implemented prior to approval of this NDA 212035:

A. Revise the product title on carton labels and container labeling to incorporate the concentration (0.9%) of the vehicle (sodium chloride) Per *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products* Guidance. Revise to "Argatroban in 0.9% Sodium Chloride Injection".

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[a] Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM592850.pdf

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/s/

CASMIR I OGBONNA
02/13/2019 11:54:06 AM

HINA S MEHTA
02/13/2019 02:26:29 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	December 4, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212035
Product Name and Strength:	Argatroban injection in 0.9% sodium chloride, 50 mg/50 mL (1 mg/1 mL)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	November 28, 2018
OSE RCM #:	2018-896-01
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container labeling for argatroban injection in 0.9% sodium chloride (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton and container labeling for argatroban injection in 0.9% sodium chloride are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Ogbonna C. Label and Labeling Review for argatroban injection in 0.9% sodium chloride (NDA 212035). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-896.

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/s/

CASMIR I OGBONNA
12/04/2018

HINA S MEHTA
12/06/2018

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)

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Date of This Review:	October 12, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212035
Product Name and Strength:	Argatroban injection in 0.9% sodium chloride, 50 mg/50 mL (1 mg/1 mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	April 30, 2018
OSE RCM #:	2018-896
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the prescribing information (PI), carton and container labeling to determine if it is acceptable from a medication error perspective as a part of their evaluation of the 505(b)(2) submission for argatroban injection in 0.9% sodium chloride (NDA 212035).

1.1 REGULATORY HISTORY

Argatroban is marketed by various manufacturers as [redacted] (b) (4) [redacted] (b) (4) The Applicant states their proposed product Argatroban injection in 0.9% sodium chloride, 50 mg/50 mL is identical to Reference Listed Drug (RLD) Argatroban injection in 0.9% Sodium Chloride, [redacted] (b) (4) in route of administration, dosage form, concentration of drug substance and indications.

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 – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed PI, carton and container labeling for areas of vulnerability in regards to medication error.

We identified areas of concern in the PI in addition to the carton and container labeling that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. Dosage and Administration Section
      a. Consider stating numbers greater than or equal to 1,000 in tables 2 and 3 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g. 1,000 mg instead of 1000 mg, 10,000 units instead of 10000 units), per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.
      b. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
         - In Section 2.3, replace the symbol "≥" with the intended meaning to prevent misinterpretation and confusion.

4.2 RECOMMENDATIONS FOR ACCORD HEALTHCARE INC.

We recommend the following be implemented prior to approval of this NDA 212035

A. Carton Labeling and Container Label
   1. The strength statement in white font with a lime green background is difficult to read. We recommend either changing the background color in the strength statement or changing the font color to increase readability of the strength.
   2. We recommend revising the font of the dosage form (i.e. Injection) to be the same size as the established name to prevent confusion.
   3. We recommend revising the usual dosage statement from "(b) (4) (b) (4)" to "See Prescribing Information" for increased clarity.
   4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if

only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

5. Bold "Do not dilute prior to administration" to increase the prominence of this important information.

B. Carton Sticker Label:

1. See A.2, A.3., and A.4.
2. We recommend adding the statement "Do not dilute prior to administration" to ensure this important information is not overlooked.
3. Relocate the net quantity statement (i.e. 10 Single Dose Vials) away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Per Draft Guidance: Container and Carton, April 2013 (lines 461-463).
4. Consider adding the statement "Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Argatroban injection received on April 30, 2018 from Accord Healthcare Inc, and the listed drug (LD).

Table 2. Relevant Product Information for Argatroban and the Listed Drug		
Product Name	Argatroban in 0.9% sodium chloride	Argatroban in 0.9% sodium chloride
Initial Approval Date	N/A	(b) (4)
Active Ingredient	Argatroban	Argatroban
Indication	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Route of Administration	Intravenous infusion	Intravenous infusion
Dosage Form	Injection	Injection
Strength	1 mg/mL, 50 mL	1 mg/mL, (b) (4)
Dose and Frequency	• Argatroban 50 mg in 50 mL aqueous sodium chloride solution (1 mg/mL) is intended for administration to adult patients • Discontinue all parenteral anticoagulants before administering Argatroban Injection in 0.9% Sodium Chloride • Adjust dosing in patients with HIT who have moderate or severe hepatic impairment	• Argatroban (b) (4) (b) (4) aqueous sodium chloride solution (1 mg/mL) is intended for administration to adult patients • Discontinue all parenteral anticoagulants before administering Argatroban Injection • Adjust dosing in patients with HIT who have moderate or severe hepatic impairment Heparin-Induced Thrombocytopenia

	Heparin-Induced Thrombocytopenia The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/ kg/min administered as a continuous infusion • Discontinue heparin therapy and obtain a baseline aPTT before administering Argatroban • After the initial dose of Argatroban, the dose can be adjusted as clinically indicated Percutaneous Coronary Intervention The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes • Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds Monitoring therapy and dosage adjustments recommendations should be followed • See special dosing recommendations for hepatic and renal impaired patients	The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered a s a continuous infusion • Discontinue heparin therapy and obtain a baseline aPTT before administering Argatroban • After the initial dose of Argatroban, the dose can be adjusted as clinically indicated Percutaneous Coronary Intervention The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes • Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds • Monitoring therapy and dosage adjustments recommendations should be followed • See special dosing recommendations for hepatic and renal impaired patients
How Supplied	The proposed drug product is supplied as a single dose vial containing 50 mg argatroban in	The reference listed drug product is supplied as a single use vial containing (b) (4)

	50 mL of aqueous sodium chloride solution (1 mg/mL). The vial is sealed with a gray rubber stopper and a green aluminum flip-off seal. • NDC 16729-430-11 – Package containing one vial of Argatroban Injection in 0.9% Sodium Chloride (each vial contains 50 mg of argatroban). • NDC 16729-430-43 – Package containing 10 vials of Argatroban Injection in 0.9% Sodium Chloride (each vial contains 50 mg of argatroban).	argatroban in (b) (4) aqueous sodium chloride solution (1 mg/mL). (b) (4) (b) (4)
Storage	Store the vials at 20ºC to 25ºC (68ºF to 77°F) [see USP Controlled Room Temperature]. Protect from light and store in original carton. DO NOT FREEZE.	Store the vials in original cartons at 20º-25ºC (68º-77°F) [see USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 20, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Argatroban in 0.9% sodium chloride. Our search identified one previous review[a], and we confirmed that our previous recommendations were implemented

[a] Maslov, Y. Label and Labeling Review for Argatroban in 0.9% sodium chloride (NDA 201743, and NDA (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010DEC13. RCM No.: 2010-1010, and 2010-1341.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 20, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR
Search Strategy and Terms	Match Exact Word or Phrase: Argatroban

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Argatroban in 0.9% sodium chloride.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

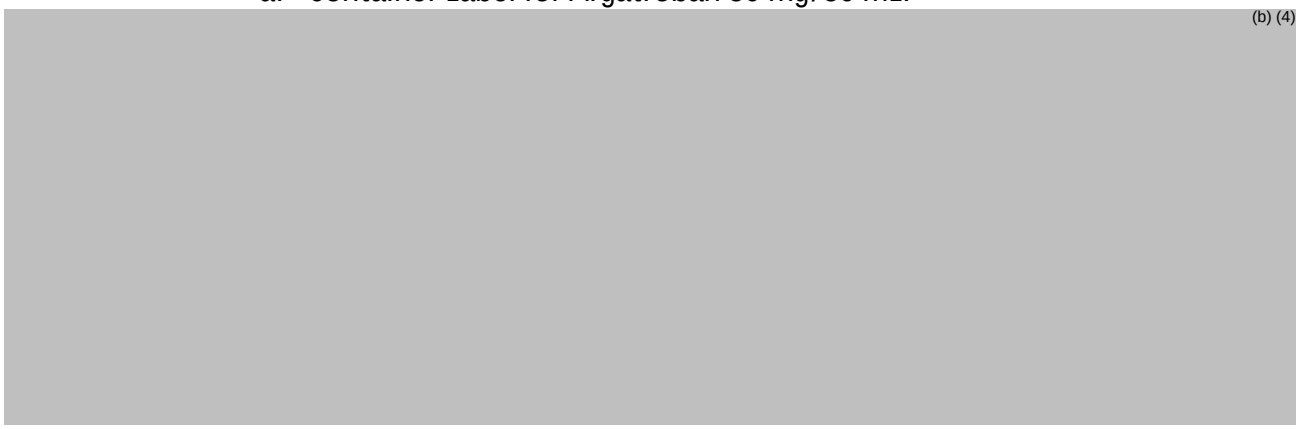
Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Argatroban injection labels and labeling submitted by Accord Healthcare Inc.

- Container label received on April 30, 2018
- Carton labeling received on April 30, 2018
- Prescribing Information received on April 30, 2018
  \\cdsesub1\evsprod\nda212035\0001\m1\us\draft-labeling-text-word.docx

G.2 Label and Labeling Images

a. Container Label for Argatroban 50 mg/50 mL:

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CASMIR I OGBONNA
10/13/2018

HINA S MEHTA
10/16/2018

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	**NDA 212035**
Applicant	**Accord Healthcare**
Proprietary Name **(nonproprietary name)**	**Argatroban Injection in 0.9% Sodium Chloride**
Receipt Date	**4/30/18**
PDUFA Goal Date **(Internal Goal Date)**	**02/28/19**
Review Classification	**Standard**
Proposed Indication (or current indication if unchanged)	**Existing argatroban indications**
Dosing Regimen	**Existing dosing for listed drug**
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application:

Accord Healthcare, Inc. has submitted a new drug application for Argatroban Injection in 0.9% Sodium Chloride (supplied as a 50 mL single-dose glass vial containing a 1 mg/mL concentration of argatroban) under section 505(b)(2). The Applicant is relying upon FDA's prior findings of efficacy and safety for the Argatroban product by (b) (4) listed as a Referenced Listed Drug and Reference Standard in the Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).

Documents Reviewed:

In this review, I propose labeling recommendations and edits in the Argatroban Injection in 0.9% Sodium Chloride labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Argatroban Injection in 0.9% Sodium Chloride.

The following pages contain the working version of the Argatroban Injection in 0.9% Sodium Chloride labeling with my recommended edits and comments (identified as 'KV1' through 'KV25') and

includes comments and edits from other review team members. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Argatroban Injection in 0.9% Sodium Chloride labeling.

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/s/

VIRGINIA E KWITKOWSKI
10/05/2018