CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208385Orig1s000

OTHER REVIEW(S)

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)

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Date of This Review:	May 9, 2017
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 208385
Product Name and Strength:	daptomycin for injection ; 350 mg per vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sagent Pharmaceuticals, Inc.
Submission Date:	March 24, 2017
OSE RCM #:	2015-2300-2
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMO

On March 24, 2017, Sagent Pharmaceuticals submitted their response to the Agency's Complete Response Letter dated June 23, 2016 as a class 2 resubmission to pending NDA 208385. The Division of Anti- Infective Products (DAIP) requested that we review the revised container label and carton labeling for daptomycin for 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 previous label and labeling reviews.[1,2]

2 DISCUSSION

We note the Applicant has addressed our previous recommendation and we find them acceptable. However, during our recent routine postmarket surveillance, we identified medication error reports that describe improper storage and use of an incorrect diluent to reconstitute daptomycin for injection. We note there are two different formulations of daptomycin for injection available on the market. These formulations differ in storage conditions throughout the medication use process (*storage of the original packages, the stability of reconstituted solution, and the stability of the diluted solution*) and reconstitution diluent. The proposed daptomycin for injection and the reference listed drug (RLD), Cubicin, should be reconstituted with 0.9% sodium chloride for injection, and stored in the refrigerator. In contrast, the new formulation, Cubicin RF, which was approved in July 2016, should be reconstituted with sterile water or bacteriostatic water for injection and stored at room temperature.

Based on our review of these cases, we recommend revisions to the proposed container labels and carton labeling for daptomycin for injection to increase clarity and prominence of reconstitution directions and the storage requirements to promote safe use of these products.

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[1] Kolejian, S. Label and Labeling Review for daptomycin for injection (NDA 208385) 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 APR 25. 32 p. OSE RCM No.: 2015-2300.

[2] Kolejian, S. Label and Labeling MEMO for daptomycin for injection (NDA 208385) 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); 2016 JUN 8. OSE RCM No.: 2015-2300-1.

3 CONCLUSION

The proposed labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product (See recommendations in section 3.1 and section 3.2).

3.1 COMMENTS FOR THE REVIEW DIVISION

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

A. Prescribing Information

1. We recommend adding a statement "There are two formulations of daptomycin that have differences concerning storage and reconstitution. Carefully follow the reconstitution and storage procedures in labeling" to section 2.5 (Preparation of Daptomycin for Injection for Administration) of the proposed PI for daptomycin for injection, to promote safe use of this product throughout the medication use process.

3.2 RECOMMENDATIONS FOR SAGENT PHARMACEUTICALS

Our routine postmarket surveillance identified medication error reports that describe improper storage and use of an incorrect diluent to reconstitute daptomycin for injection. To increase clarity and prominence of important information, we recommend the following:

A. Container Label

1. Add the statement, "Must be refrigerated" to the principal display panel of the container label. The statement must be prominent, you can achieve this by highlighting and placing a box around the statement.

2. Relocate and bold the reconstitution statement "Reconstitute with 7 ml of 0.9% sodium chloride for injection to (b) (4) 50 mg per ml (b) (4)." to appear on the top of the side panel.

B. Carton Labeling (single pack, multiple pack)

1. See A.1 above.
2. See A.2 above.
3. Add the statement, "Reconstitute with 7 ml of 0.9% sodium chloride for injection to (b) (4) 50 mg per ml (b) (4)" to the principal display panel of the carton labeling.

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/s/

SEVAN H KOLEJIAN
05/09/2017

OTTO L TOWNSEND
05/10/2017

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:	April 25, 2016
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 208385
Product Name and Strength:	daptomycin for injection ; 350 mg per vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sagent Pharmaceuticals, Inc.
Submission Date:	August 25, 2015
OSE RCM #:	2015-2300
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

The Division of Anti –Infective Products (DAIP) requested that we review the container label, carton labeling (See Appendix G), and Full Prescribing Information (FPI) for daptomycin for injection, 350 mg per vial, to determine if they are acceptable from a medication error perspective.

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	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Prescribing information (FPI)	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

Daptomycin for injection is currently available on the market as follows:

- CUBICIN (Daptomycin for Injection), 500 mg per vial, NDA 021572, held by Cubist Pharmaceuticals Inc., and approved on September 12, 2003.
- Daptomycin for injection, 500 mg per vial, ANDA 202857, held by Hospira Inc. and approved on September 12, 2014.
- Daptomycin for injection, 350 mg per vial, NDA 203797, held by Hospira Inc. and tentatively approved on February 10, 2015.

Sagent Pharmaceuticals, Inc. submitted a 505(b)(2) New Drug Application for Daptomycin for Injection, 350 mg per vial for intravenous use with the same active ingredient, final concentration after reconstitution, indication, route of administration, dosage form, and dosing regimen as the reference drug, Cubist 's CUBICIN (NDA 021572). However, the proposed product will have different total amount of drug per vial (350 mg vs. 500 mg) and vial size (15 ml vs. 10 mL) from the reference drug. Thus, the contents of the vial will be reconstituted with 7 ml (instead of 10 mL) of 0.9% sodium chloride injection to yield a final concentration of 50 mg/mL of reconstituted daptomycin for injection. Since the dosing for daptomcyin is always weight based (e.g., 4mg per kg), we do not have any safety concerns with the introduction of the proposed product to the market. However, we are concerned that there may be preparation errors and provide recommendations in section 4.1 to safely address differences in the reconstitution process from the reference product.

Labels and Labeling

We performed a risk assessment of the proposed labels and labeling for daptomycin for Injection, 350 mg per vial to identify deficiencies that may lead to medication errors and for areas of improvement. Our review of the proposed container label and carton labeling (Appendix G) identified areas of improvement. In section 4.1, we provide additional recommendations to mitigate confusion and promote the safe use of this product.

Our review of the Revised Full Prescribing Information (FPI), submitted on April 12, 2016, *Dosage and Administration, Dosage Forms and Strengths and How it Supplied sections of* the FPI identified areas of improvement. We noted that error-prone abbreviations "IV" is used throughout the FPI that may pose confusion to the prescriber. In section 4.1, we provide additional recommendations to mitigate confusion and promote the safe use of this product.

We note that the package type term (b) (4) vial is used in labels and labeling for this proposed product. We informed the Office of Pharmaceutical Quality (OPQ) and defer to them to determine the appropriate package type term.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the introduction of the Daptomycin for injection, 350 mg per vial, does not possess safety risk from the medication error perspective. However, the proposed labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Janet Higgins, OSE Project Manager, at 240-402-0330.

4.1 RECOMMENDATIONS FOR THE DIVISION

We advise the following recommendations be implemented prior to approval of this NDA:

Full Prescribing Information:

1. Revise abbreviated "IV" route of the administration to read "For Intravenous Use or intravenously" throughout the document[1].

2. Add the statement "Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose in patients where a total dose is less than 350 mg throughout the document where applicable.

3. In section 2.5, Preparation of daptomycin for Administration, to improve readability, consider adding subheadings 2.6 as follows:

   2.6 Administration Instructions

   Intravenous injection over a period of 2 minutes

   For intravenous (IV) injection over a period of 2 minutes, administer the appropriate volume of the reconstituted daptomycin (concentration of 50 mg/mL).

   Intravenous infusion over a period of 30 minutes

   For intravenous infusion over a period of 30 minutes, the appropriate volume of the reconstituted daptomycin (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection.

[1]Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013, lines [478-484]. Available from http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4.2 RECOMMENDATIONS FOR THE SAGENT PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 208385.

A. <u>Container Label</u>

1. Revise the statement from "**For Intravenous Use Only"** to read **"Must be reconstituted. For Intravenous Use Only"** we recommend this to promote the safe use and to provide clarity of important product preparation and administration information.
2. Add the statement "Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose in patients where a total dose is less than 350 mg.
3. On the side panel, add clarifying statement similar to "Reconstitute with 7 ml of 0.9% sodium chloride injection to (b) (4) 50 mg /ml (b) (4)" consider highlighting the statement to promote safe use of this product.

B. <u>Carton labeling for single pack and multiple pack.</u>

1. See A.1 above.
2. See A.2 above.
3. Revise the statement "Reconstitute Daptomycin for Injection with 0.9% sodium chloride injection" to read "Reconstitute Daptomycin for Injection with 7 ml of 0.9% sodium chloride injection for clarity and to promote safe use of this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Daptomycin for injection; 350 mg per vial that Sagent Pharmaceuticals, Inc. submitted on November 23, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Daptomycin for injection and the Listed Drug		
Product Name	Daptomycin for injection	Reference Listed Drug Cubicin (daptomycin) for injection (NDA 021572)
Initial Approval Date	N/A	September 12, 2003
Active Ingredient	Daptomycin	
Indication	indicated for the treatment of: • Complicated skin and skin structure infections (cSSSI) • *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis.	
Route of Administration	Intravenous	
Dosage Form	Lyophilized powder for reconstitution in a single-use vial.	
Strength	350 mg per vial (after reconstitution 50 mg /ml)	500 mg per vial (after reconstitution 50 mg /ml)
Dose and Frequency	4mg/kg to 6 mg/kg once every 24 hour or every 48 hours for renal impairment. .	
How Supplied	supplied as follow: • NDC 25021-179-15; 350 mg Single (b) (4) Vial, 1 vial per carton • NDC 25021-179-16; 350 mg Single (b) (4) Vial, 10 vials per carton.	supplied as a sterile pale yellow to light brown lyophilized cake in a single-use 10 mL vial containing 500 mg of daptomycin: Package of 1 (NDC 67919-011-01).
Storage	Store original packages at refrigerated temperatures, 2 to 8°C (36 to 46°F); avoid excessive heat.	
Container Closure	15 ml vial glass vial.	10 ml vial glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 30, 2015, we searched the L:drive and AIMS using the terms, daptomycin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[2,3]RCM # (b) (4) 2014-2635 for Cubicin (daptomycin) for injection, NDA21572, submitted by Cubist Pharmaceuticals. However, the recommendation in previous review was not relevant to current review of daptomycin for injection label and labeling.

[2] Kolejian S. Review of Revised Label and Labeling Memorandum for Cubicin (daptomycin) for injection(NDA 21572; S-048). 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 FEB 5. OSE RCM No.: 2014-2635.

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APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 30, 2015, 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 Newletter(s)	Acute Care, Community, Nursing, ISMP Medication Safety Alert
Search Strategy and Terms	Match Exact Word or Phrase: Daptomycin

D.2 Results

Our search of ISMP newsletters resulted in the following newsletter articles on daptomycin for injection.

ISMP Medication Safety Alert, Vol. 8, No. 22 October 30, 2003, Page 1
ISMP Medication Safety Alert, Vol. 8, No. 25 December 18, 2003, Page 2
ISMP Medication Safety Alert, Vol. 9, No. 2 January 29, 2004, Page 4
ISMP Medication Safety Alert, Vol. 10, No 24 December 1, 2005, Page 2
ISMP Medication Safety Alert Vol. 14, No. 1 January 15, 2009, Page 2
ISMP Medication Safety Alert, Vol. 11, No 2 January 26, 2006, page 5

These articles have been identified and assessed previously in our OSE review # 2014-2635[4]. We note that the look-alike /sound-alike potential between daptomycin and dactinomycin has already been identified and the names are on the ISMP List of Confused Names[5]. In addition, mix up between Daptomycin and Dactinomycin have been reviewed previously as a potential signal in OSE review # 2009-586, dated May 26, 2009 and concluded to continue to monitor these wrong drug errors between Daptomycin and Dactinomycin to determine if any additional action is warranted. Our review did not identify any new cases.

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[4] Kolejian S. Label and Labeling Review for Cubicin (NDA 21572; S-048). 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 JAN 15. 3 p. OSE RCM No.: 2014-2635.

[5] ISMP's List of Confused Names Available at: https:// http://www.ismp.org/tools/confuseddrugnames.pdf. Accessed: December 30, 2015.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 5, 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.[6]

Table 3: FAERS Search Strategy	
Date Range	**01/01/2015 to 01/05/2016**
Product	**Daptomycin** [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)

E.2 Results

Our search identified one case (Case # 11843971) that describes incorrect dose error (n=1) as described in section E.3 bellow. We note that Daptomycin for injection is dosed based on

[6] 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.

patient weight (4 mg /kg or 6 mg/ kg every 24 hours or 48 hours) as stated in Dosage and Administration section of the FPI for currently marketed daptomycin for injection products. No additional information provided to determine the root cause for patient receiving additional dose. Thus, DMEPA does not recommend any labeling changes based on this case at this time.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	FDA Initial Recd Date	FDA Recd Date	Narrative
11843971	12/16/2015	12/16/2015	Narrative: Patient began daptomycin 1000mg every 48 hrs for bacteremia ands endocarditis on 12/4/15 and discharged on 12/11. On 12/14/15 patient reported to the ER with angioedema that was attributed to the daptomycin. Of note, the patient was to receive 1000mg every 48hrs but according to the MAR in CPRS he received 1000mg on the 10th and 11th. Patient received methylprednisolone, famotidine and diphenhydramine for the treatment of angioedema. He remained on methylprednisolone 125mg every 6 hours while in the MICU. Symptoms: Symptoms: 1. Angioedema Suspect Drug # 1 Dosing: 1000mg IV every 48 hours. Dosed following dialysis Treatment Drugs Used: 1 - METHYLPREDNISOLONE Dose: 125 Units: MG Freq: QID Route: IV 2 - DIPHENHYDRAMINE Dose: 25 Units: MG Freq: PRN Route: IV 3 - FAMOTIDINE Dose: 20 Units: MG Freq: ONCE Route: IV

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. Prescribing Information submitted on April 12, 2016

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