CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208385Orig1s000

CLINICAL REVIEW(S)

Clinical Review of Resubmission for NDA 208385

NDA 208385	505(b)(2)
Applicant	Sagent Pharmaceuticals, Inc
Date of Resubmission	March 24, 2017
PDUFA Goal Date **Action Date**	September 24, 2017 September 22, 2017
Proprietary Name of Drug Product Drug	Daptomycin for Injection
Dosage form(s)/Strength(s)	350 mg lyophilized cake or powder for reconstitution in a single-use vial
Route of Administration	Intravenous
Applicant Proposed Indication(s)/Population(s)	Complicated Skin and Skin Structure Infections; *Staphylococcus aureus* Bloodstream Infections (Bacteremia) Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates/ Adult Patients
Clinical Reviewer	Alma Davidson, M.D.
Clinical Team Leader	Hala Shamsuddin, M.D.
Recommendation on Regulatory Action	Approval from the clinical perspective

1. Background

On June 23, 2016, this application was given a Complete Response (CR) by the FDA because of product quality issues including manufacturing facility deficiencies, unexplained (b) (4) the bulk solution, and the proposed acceptance criteria for individual impurities/ related substances (b) (4) in the drug product specification are too wide and not adequately justified. The CR letter also recommended a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

2. Chemistry, Manufacturing, and Control (CMC)

Please refer to the CMC review by Dr. Shrikant Pagay for comments and recommendations.

3. Clinical Review of Safety Update

The applicant provided a brief overview summary of significant findings in the safety profile of daptomycin. The applicant states that the adverse events (AEs) that were reported in the Cubicin® Prescribing Information (July 2016), contained in their Literature References and AERS summary-July 28, 2016 (AERS Counts by Preferred Term) can be considered expected adverse events, since they are part of the reported AE profile. In addition to these expected AEs, other unexpected AEs were also reported to the AERS.

The 46 AEs most often reported to the AERS (representing 2.66% to 0.44% of the total AERS reports) are presented in the table below.

Table 1: The 46 Adverse Events Most Often Reported to the AERS or FAERS

Preferred Term	Frequency Count from AERS	Percent of Total Frequency from AERS
Death	67	2.6576
Pyrexia	50	1.9833
Acute kidney injury	46	1.8246
Drug ineffective	43	1.7056
Eosinophilic pneumonia	43	1.70567
Blood creatine phosphokinase increased	37	1.46767
Eosinophilia	34	1.34867
Pneumonia	34	1.34867
Rash	31	1.22967
Nausea	27	1.07100
Renal failure	26	1.03134
Dyspnea	24	0.95200
Interstitial lung disease	23	0.91234
Respiratory failure	23	0.91234

Preferred Term	Frequency Count from AERS	Percent of Total Frequency from AERS
Renal impairment	22	0.87267
Drug reaction with eosinophilia and systemic symptoms	22	0.87267
Sepsis	20	0.79334
Rhabdomyolysis	20	0.79334
Diarrhea	19	0.75367
Antimicrobial susceptibility test resistant	19	0.75367
Eosinophilic pneumonia acute	19	0.75367
Vomiting	18	0.71400
Drug resistance	18	0.71400
Hemoglobin decreased	17	0.67434
White blood cell count decreased	16	0.63467
Fatigue	15	0.59500
Treatment failure	15	0.59500
Infection	15	0.59500
Cough	15	0.59500
Hypotension	15	0.59500
Atrial fibrillation	14	0.55534
Staphylococcal infection	14	0.55534
Multi-organ failure	13	0.51567
Blood creatinine increased	13	0.51567
White blood cell count increased	13	0.51567
Hyperkalemia	13	0.51567
Pruritus	13	0.51567
Neutropenia	12	0.47600

Preferred Term	Frequency Count from AERS	Percent of Total Frequency from AERS
Asthenia	12	0.47600
Cellulitis	12	0.47600
Osteomyelitis	12	0.47600
Malaise	11	0.43633
Hepatocellular injury	11	0.43633
Endocarditis	11	0.43633
Platelet count decreased	11	0.43633
Erythema	11	0.43633

Applicant's Conclusions of Clinical Safety

- The Cubicin® Prescribing Information (July 2016), postmarketing data from the AERS search, and the published literature searches support the safety and tolerability of daptomycin for the treatment of gram-positive bacterial infections.

- Overall, the AEs described in the Cubicin® Prescribing Information (July 2016) are similar to those observed in the AERS search and published literature searches.

- The most common AEs seen are elevations in CPK and other liver enzymes, musculoskeletal AEs (e.g., myalgia, rhabdomyolysis), respiratory AEs (e.g., dyspnea, pharyngolaryngeal pain, eosinophilic pneumonia) and renal AEs (e.g., renal impairment).

- No significant new adverse events were reported in the AERS search and literature searches performed. Thus, no new safety information needs to be added to the Cubicin® Prescribing Information (July 2016).

Reviewer's Safety Comment: Based on review of the applicant's safety update of the RLD, Cubicin®(daptomycin for injection) 500 mg/vial (July 2016), no new safety information needs to be added to the Cubicin label at the time. However, the reviewer looked at the most recently approved RLD, Cubicin® Prescribing Information (June 9, 2017) which provides the addition of "organizing pneumonia" to the WARNINGS AND PRECAUTIONS, Eosinophilic Pneumonia subsection (5.3) and ADVERSE REACTIONS, Postmarketing Experience subsection (6.2) of the Cubicin® (daptomycin for injection) label. These updated changes are added to the Daptomycin for Injection prescribing information (see below). (Please refer also to the previous clinical safety review for this application dated 05/09/2016 filed in DARRTS.)

4. Labeling Review

The following labeling issues identified in the CR letter and addressed by the applicant in this resubmission:

● Revise "(b) (4)" to "Single-Dose" wherever it appears in the prescribing information.

● Addition of the adverse reaction, "acute generalized exanthematous pustulosis" to Post-marketing Experience subsection as noted below:

"Skin and Subcutaneous Tissue Disorders: serious skin reactions, including Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement); acute generalized exanthematous pustulosis."

The following new and updated RLD, Cubicin® labeling changes are added to the applicant's proposed Daptomycin for Injection prescribing information:

● Several sections associated with adult patients information (including updating the adult adverse reactions in HIGHLIGHTS OF PRESCRIBING INFORMATION, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, CLINICAL PHARMACOLOGY, CLINICAL TRIALS, REFERENCES, and PATIENT COUNSELING INFORMATION) of the daptomycin for injection prescribing information has been updated to be consistent with the approved RLD, Cubicin® label dated 03/29/2017 with the exception of the data related to the indication of Complicated Skin and Skin Structure Infections (cSSSI) for pediatric patients (1 to 17 years of age) due to RLD's pediatric patent exclusivity which expires in March 29, 2020.

● Addition of "organizing pneumonia" to the WARNINGS AND PRECAUTIONS, Eosinophilic Pneumonia subsection (5.3) and ADVERSE REACTIONS, Postmarketing Experience subsection (6.2) to be consistent with the recently approved RLD, Cubicin® prescribing information dated June 9, 2017. (Please see clinical labeling review in DARRTS, dated June 9, 2017.)

5. Conclusion and Recommendation

From the clinical perspective, this NDA is recommended for approval pending completion of the CMC and other Product Quality issues.

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/s/

ALMA C DAVIDSON
08/16/2017

HALA H SHAMSUDDIN
08/16/2017

Clinical Review of NDA

NDA 208385	505(b)(2)
Applicant	Sagent Pharmaceuticals, Inc
Date of Submission	August 25, 2015
PDUFA Goal Date	June 24, 2016
Proprietary Name of Drug Product Drug	Daptomycin for Injection
Dosage form(s)/Strength(s)	350 mg lyophilized cake or powder for reconstitution in a single-use vial
Route of Administration	Intravenous
Applicant Proposed Indication(s)/Population(s)	Complicated Skin and Skin Structure Infections; *Staphylococcus aureus* Bloodstream Infections (Bacteremia) Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates/ Adult Patients
Clinical Reviewer	Alma Davidson, M.D.
Medical Team Leader	Hala Shamsuddin, M.D.
Recommendation on Regulatory Action	Approval

1. Introduction

Daptomycin for Injection contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. Sagent Pharmaceuticals, Inc. has submitted a 505(b)(2) New Drug Application (NDA) 208385 for Daptomycin for Injection 350 mg/vial to the FDA on August 25, 2015.

The applicant has submitted this 505(b)(2) new drug application (NDA) for Daptomycin for Injection 350 mg/vial using the Cubist/Merck product, CUBICIN® (daptomycin for injection) as the reference listed drug (RLD). The applicant's product, Daptomycin for Injection, 350 mg/vial, has the same proposed indications, dosing regimens, and age group as the RLD, CUBICIN® (daptomycin for Injection) 500 mg/vial. There are no clinical trials conducted by the applicant to support this 505(b)(2) NDA for Daptomycin for Injection 350 mg/vial. The review for this NDA relies on the prior FDA determination of effectiveness and safety of daptomycin based on studies which were not conducted by or for the applicant.

2. Chemistry, Manufacturing, and Control (CMC): Please refer to the CMC review by Dr. D. Matecka for comments and recommendations.

3. Clinical Review:

In order to support this 505(b)(2) NDA submission for daptomycin, literature searches were performed by the applicant to search for safety information regarding daptomycin use. The literature searches, extending back to 2014, were performed using two different databases to include articles published after the last revision of the Cubicin® Prescribing Information (November 2014). The databases that were used to perform the literature searches were Medline and ToxNet.

Literature Review

The applicant found relevant publications in their search. Table 1 provides the summary of reports found in the published literature which described the common adverse events observed following daptomycin treatment. These publications included open-label studies, observational studies, retrospective chart reviews, and case reports. Daily doses of daptomycin ranged from 4 mg/kg/day to 10 mg/kg/day (which is described as high dose daptomycin), and up to 12 mg/kg/day. In a number of these literature reports, daptomycin was given in combination with other antibacterials, such as nafcillin, rifampin, aztreonam, and metronidazole. Daptomycin was also been given in combination with statins. The common adverse events reported in the literature include rhabdomyolysis, myalgia, renal impairment, eosinophilic pneumonia, and nausea. In addition, increases in creatine phosphokinase (CPK) and other liver enzymes, and thrombocytopenia have been reported. These AEs are similar to those reported in the Cubicin® Prescribing Information (November 2014) and the FDA Adverse Event Reporting System (FAERS), formerly known as Adverse Event Reporting System (AERS).

Table 1: Summary of Literature Publications with Safety Reporting

Authors/Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Safety Data
Adams N, Johnson MD, Storm DW, and Maves RC/2014	Acute Focal Bacterial Nephritis Due to Methicillin-Resistant *Staphylococcus aureus* in an Immunocompetent Adult	Case report/MRSA bacteremia after a skin and soft tissue infection	8 mg/kg every 24 hours	No AE reported.
Berg ML, Estes LL, Dierkhising RA, Curran B, Enzler MJ/ 2014	Evaluation of Impact of Statin Use on Development of CPK Elevation During Daptomycin Therapy	Single-center, retrospective cohort study of patients ≥ 18 years of age who received daptomycin for ≥72 hours and had ≥1 follow-up CPK during a 5-year period	Mean (SD) daptomycin dose, in mg/kg 5.3 (1.0)	Daptomycin and statin concurrent therapy demonstrated an approximately 2-fold risk of CPK elevation compared with those having their statin therapy held, but the overall group effect was not statistically significant (P = 17); 1 case of rhabdomyolysis
Bland CM, et al./2014	Musculoskeletal Safety Outcomes of Patients Receiving Daptomycin with HMG-CoA Reductase Inhibitors	Retrospective, multicenter study of adult patients hospitalized from 2005 to 2010 who received daptomycin with or without statin therapy./ Bacteremia/endocarditis, SSSI, and bone/joint infections, including osteomyelitis.	Daptomycin dose (mean SD) (mg/kg) 6.75 ± 1.54	Higher rates of CPK elevation of 1,000 U/liter or myalgias were seen in patients receiving daptomycin with concomitant statin therapy, but this value was not statistically significant compared to rates observed in patients receiving no statin therapy.

Table 1: Summary of Literature Publications (Continued)

Authors/Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Safety Data
Bradley JS, et al/2014	Single-dose Pharmacokinetics of Daptomycin in Pediatric Patients 3–24 Months of Age	Proven or suspected bacterial infection were enrolled into 3 age groups (13–24, 7–12 and 3–6 months) for PK evaluation	Intravenous daptomycin (single dose) was infused over 30 minutes at 6 mg/kg in subjects 13-24 months of age and at 4 mg/kg in the younger age groups (3–6 and 7–12 months	Most frequently reported TEAEs were increased blood CPK (3 subjects in the 7–12 month group; 13% of the entire safety population) and constipation, teething, and pyrexia (2 subjects each, 8%). All other TEAEs were reported in 1 including 2 incidences of increased blood CPK (259 and 156 U/L) and 1 incidence each of increased alanine aminotransferase (53 U/L), increased aspartate aminotransferase (68 U/L) and rash.

Table 1: Summary of Literature Publications (Continued)

Authors/Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Safety Data
Gasch O et al,/ 2014	Emergence of Resistance to Daptomycin in a Cohort of Patients with Methicillin-Resistant *Staphylococcus aureus* Persistent Bacteremia Treated with Daptomycin.	Prospective review of cohort of patients with MRSA bacteremia	6 mg/kg	Death within 30 days was observed in 7 of 22 (32%) and microbiological failure in 9 of 22 (41%) episodes.
Hagiya H, et al/2014	Successful Treatment of Persistent MRSA Bacteremia using High-dose Daptomycin Combined with Rifampicin	Case report	High-dose daptomycin (DAP, 10 mg/kg) and rifampicin	No AE reported.
Hagiya H, et al./2014	Acute Generalized Exanthematous Pustulosis (AGEP) Caused by Daptomycin in a Critically Ill Burn Victim*	Case report	350 mg on alternate days due to renal insufficiency	Although the patient recovered from AGEP, he ultimately died of multiple organ failure and sepsis on Day 38.

* A review of AGEP cases associated with daptomycin found in FAERS are provided below under Safety Conclusion in this review.

Table 1: Summary of Literature Publications (Continued)

Authors/Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Safety Data
Hayakawa K, et al/2014	Impact of Different Antimicrobial Therapies on Clinical and Fiscal Outcomes of Patients with Bacteremia Due to Vancomycin-Resistant Enterococci	Bacteremia due to VRE *faecalis* and *faecium*	6 mg/kg (range, 6 to 12 mg/k	CPK elevation and thrombocytopenia
Klibanov OM et al/2014	Successful Treatment of Infective Panniculitis With Daptomycin in a Pregnant, Morbidly Obese Patient.	Case report	4 mg/kg (800 mg) IV every 24 hours	No AE reported.
Kullar R, et al/2014	Efficacy and Safety of Daptomycin in Patients with Renal Impairment: A Multicenter Retrospective Analysis	Retrospective observational case series; Gm positive skin infections	4 mg/L	CPK elevation; 2 patients died (one due to septic shock and cardiac arrest attributed to bacteremia.; and the other died due to infection)
Len O, et al/2014	Daptomycin is Safe and Effective for the Treatment of Gram-Positive Cocci Infections in Solid Organ Transplantation.	Observational cohort, open label study/ Catheter-related bacteremia caused by coagulase-negative staphylococci, skin infection caused by *Staphylococcus aureus*, and intra-abdominal abscess caused by *E. faecium*	6 mg/kg; 8 mg/kg; and >8 mg/kg	CPK elevation. Three deaths were reported as unrelated to daptomycin
Liang SY, et al/2014	Daptomycin Versus Vancomycin for Osteoarticular Infections Due to Methicillin-Resistant *Staphylococcus aureus* (MRSA): A Nested Case–Control Study	Case-control study; MRSA osteomyelitis or septic arthritis	6.0 (± 0.6) mg/kg	CPK elevation

Table 1: Summary of Literature Publications (Continued)

Authors/Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Daptomycin Safety Data
Lora-Tamayo J, et al/2014	High Doses of Daptomycin (10 mg/kg/d) Plus Rifampin for the Treatment of Staphylococcal Prosthetic Joint Infection Managed with Implant Retention: A Comparative Study	Observational retrospective multicenter study/Prosthetic Joint Infection	8.3 to 12.5 mg/kg/d	Acute renal injury and rhabdomyolysis
Marc F,et al/2014	A Retrospective Study of Daptomycin Use in a Paris Teaching-Hospital.	Retrospective descriptive study	5 mg/kg to 10 mg/kg	Severe thrombocytopenia; severe rhabdomyolysis with high CPK level, and suspected cutaneous toxicity. Other AEs such as nausea, acute renal impairment, and mild rhabdomyolysis were observed but did not lead to treatment discontinuation. Two patients died (female patients 7 and 21), respectively after11 days of treatment for endocarditis due to MRSA, and 79 days of treatment for acute recurrence of chronic sepsis.
Montange D, et al/2014	Penetration of Daptomycin into Bone and Synovial Fluid in Joint Replacement	Phase I, open label, non-randomized study/ knee or hip replacement and received a single intravenous dose of 8 mg of daptomycin per kg of body weight between 4 and 12 hours prior to surgery	8 mg/L	One serious adverse event occurred (bullous pemphigoid) diagnosed 28 days after surgery.

Table 1: Summary of Literature Publications (Continued)

Authors/ Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Daptomycin Safety Data
Ng JK,, et al/2014	Daptomycin Dosing Based on Ideal Body Weight Versus Actual Body Weight: Comparison of Clinical Outcomes	Retrospective/ Treatment of enterococcal infections and Staphylococcal infections	4 mg/kg and 6 mg/kg	CPK elevation. Presumed daptomycin pulmonary toxicity. Eosinophilia.
Pasticci MB,et al/2014	Tolerability and Efficacy of Long-Term Treatment with Daptomycin, Ceftazidime and Colistin in a Patient with a Polymicrobial, Multidrug-Resistant Prosthetic Joint Reinfection: A Case Report	Case report/ Prosthetic Joint Infection	500 mg per day	No AE reported.
Patel JJ, et al/2014	Daptomycin-induced Acute Eosinophilic Pneumonia	Case report/ bilateral calcaneal osteomyelitis	Dose not reported	Acute eosinophilic pneumonia
Pea F, et al/2014	Daptomycin Underexposure in a Young Intravenous Drug User who was Affected by Life-Threatening *Staphylococcus aureus*-Complicated Skin and Soft Tissue Infection Associated with Bacteremia	Case report/MSSA Skin infection with bacteremia	8 mg/kg q24 h IV over 30 minutes	No AE reported.
Rolston KVI, et al/2014	Daptomycin Use in Neutropenic Patients with Documented Gram-Positive Infections	Retrospective study/Catheter-related bacteremia, non-catheter-related bacteremia; skin and skin structure infections, urinary tract infections /pyelonephritis , bone/joint infections, endocarditis	6 mg/kg (3.6, 8.3)	Elevated blood CPK, neutropenia, pain in extremity, renal failure, back pain, chromaturia, clostridium colitis, liver function test abnormal, and hyperbilirubinemia.

Table 1: Summary of Literature Publications (Continued)

Authors/ Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Daptomycin Safety Data
Sakoulas G, et al/2014	Nafcillin Enhances Innate Immune-Mediated Killing of Methicillin-Resistant *Staphylococcus aureus*	Case study/ refractory MRSA bacteremia due to sacral osteomyelitis	10 mg/kg/day	No AE reported.
Tatarelli P, et al/2014	Efficacy of Daptomycin Lock Therapy in the Treatment of Bloodstream Infections Related to Long-Term Catheter. Infection	Retrospective review/ Catheter-related Blood stream Infection (CRBSI)	8 mg/kg daily.	No AE reported.
Tosti R, et al/ 2014	Emerging Multidrug Resistance of Methicillin-Resistant Staphylococcus aureus in Hand Infections.	Retrospective chart review/MRSA in hand infections	Dose not reported.	N/A
Usery JB, et al/.2015	Evaluation of the Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia	Retrospective study/MRSA bacteremia	6.7 ± 1.8 mg/kg/day	Adverse effects were reported but unspecified.
Vandenhende M-A, et al/2014	Successful Daptomycin Lock Therapy for implantable Intra-Arterial Catheter Infection in a Patient with Liver Metastases of Colon Cancer	Case report/Device infection	10 mg/kg q daily for 14 days plus a lock therapy (5 mL of a solution containing 5 mg/mL of dapto	Moderate elevation of liver enzymes and of CPK from day 10 (lower than 1.5 times the upper level of normal) without myalgia.

Table 1: Summary of Literature Publications (Continued)

Authors/ Publication Year	Article Title	Study Design/ Indication/	Daptomycin Dose	Daptomycin Safety Data
Walter V, et al/2014	Eradication of a Chronic Wound and Driveline Infection After Redo-LVAD Implantation.	Case report/MRSA exit driveline wound Infection	Not provided	No AE reported.
Weston A,,et al/2014	The Efficacy of Daptomycin Versus Vancomycin for Methicillin-Resistant Staphylococcus aureus Bloodstream Infection in Patients With Impaired Renal Function	Retrospective cohort study/MRSA bacteremia	6.8 mg/kg (range, 5.1-10.8 mg/kg)	CPK elevations > 1000 IU/L, leading to cessation of the drug.
Yuste JR, et al/2014	Daptomycin in the Treatment of Prosthetic Joint Infection by *Enterococcus faecalis:* Safety and Efficacy of High-Dose and Prolonged Therapy.	Case report/ Prosthetic joint infection due to *E. Faecalis*	10 mg/kg/day	Repeated peripheral phlebitis

Safety Conclusion:

The most common AEs reported in the literature and observed in FAERS are elevations in CPK and other liver enzymes, musculoskeletal AEs (e.g., myalgia, rhabdomyolysis), respiratory AEs (e.g., dyspnea, pharyngolaryngeal pain, eosinophilic pneumonia) and renal AEs (e.g., renal impairment). These adverse events are already listed in the current Cubicin® prescribing information. However, one adverse reaction reported in the literature but not labeled is acute exanthematous pustulosis (AGEP) that developed in a critically ill burn patient who received daptomycin.[2] This AR is not labeled in the current daptomycin prescribing information and deserves to be mentioned under the Postmarketing Experience subsection of the daptomycin label.

Additional Review of Acute Generalized Exanthematous Pustulosis (AGEP) Cases reported in FAERS is provided below:

AGEP is a pustular reaction that is primarily drug induced in 90% of cases and characterized by acute, extensive, small, nonfollicular, sterile pustules that usually begin in intertriginous folds with widespread edema and erythema. It is a rapidly progressing, self-limiting disease with a

good prognosis. It frequently occurs as a reaction to antibacterials, commonly penicillins and macrolides. AEP is considered to be similar to severe drug-induced skin reactions, such as drug-induced hypersensitivity syndrome or Stevens-Johnson syndrome. Its prognosis is generally favorable.[2-7]

Recent literature publications regarding safety information of daptomycin reported cases of daptomycin-induced AGEP. AGEP is not mentioned in the daptomycin full prescribing information and needs to be explored as an adverse reaction possibly associated with daptomycin therapy. The FAERS database and the RLD, Cubicin® Periodic Safety Update Report (PSUR) was searched for reports of AGEP related to daptomycin use.

The reviewer found cumulative five events in PSUR (2013-2014), and one case of AGEP from the PSUR (2014-2015) and some cases of AGEP associated with daptomycin use in FDA Expedited Reporting System (FAERS). An initial search in FAERS retrieved 26 cases. After looking further at these cases, only 10 were unique cases. Demographics and other information of the 10 cases are summarized in Table 2. Five of the 10 cases are both spontaneous and literature reports, and six cases are spontaneous reports, as summarized in Table 3.

Table2: Demographics and clinical characteristics of cases of AGEP in association with Daptomycin

Age in years (range)	70 years (56 – 86)
Gender (n)	Male: 8 Female: 2
Source (n)	USA: 4 Japan: 2 France:2 Brazil: 1 Singapore:1
Indication for Daptomycin (n)	Complicated SSTI: 1 Endocarditis: 2 Bacteremia: 1 Off-label Use:5 Unknown: 1
Dose (n)	Known[a] 7 Unknown: 3
Time to onset	Variable
Outcome (n)	Unknown: 3 Recovered: 6 Died:2
Positive Dechallenge (n)	Unknown: 9 Yes: 1

a = Dosage amounts ranged from 350mg to 750 mg q day

Table 3: Acute Generalized Exanthematous Pustulosis Cases Associated with Daptomycin (Continued)

Case Number	Age/Gender/ Country	Indication	Onset of Skin Eruption	Suspect Medication(s)	Daptomycin Dose	Oucome/Causality Assessment
1 12541 Version #2 Literature report: Hagiya H, et al: AGEP Caused by Daptomycin in a Critically Ill Burn Victim.	77 yo/M/ Japan	Burn skin site MRSA infection	3 days after dapto; Positive Dechallenge	Daptomycin	350 mg q 48h	On an unknown date, skin eruption disappeared after daptomycin was discontinued. The patient recovered from AGEP. Reporting physician considered AGEP as related to daptomycin with no other causative factors. Confirmed by skin biopsy. However, on day 38 of hospital stay, the patient died of multiple organ failure and sepsis. No autopsy performed.
1 336378 Version 2 Literature report: Gordon Spratt EA, et al Daptomycin-Induced AGEP	56 yo/F/ USA	Knee replacement infection (off-label use)	4 days after dapto; Two days after discontinuing daptomycin, the rash was reported as resolving	Daptomycin	500 mg q 24 hr	In the opinion of the physician, AGEP was probably related to daptomycin. AGEP was confirmed by skin biopsy.
1 47 9 7 Version 2 /10471451 Version 1) 112736 4 Version 1 Literature report: Krishna S, et al. A rapidly progressive and fatal case of atypical AGEP	78 yo/F/ USA	Sepsis (off-label use)	Unknown	Daptomycin/ Pip-tazo; Fluconazole; Levo; Vanco	Unknown	On an unknown date, the patient developed disseminated intravascular coagulation and on hospital day 4, the patient died due to multi-organ failure. The final cause of death at autopsy was deemed multi system organ failure caused by complications of AGEP without internal sources of sepsis.

Table 3: Acute Generalized Exanthematous Pustulosis Cases Associated with Daptomycin (Continued)

Case Number	Age/Gender / Country	Indication	Onset of Skin Eruption	Suspect Medication(s)	Daptomycin Dose	Oucome/Causality Assessment
11240926 Version 1)	67yo/M/ Japan	Febrile neutropenia (off-label)	First day	Daptomycin/ Teicoplanin	350 mg qd	The reporting physician felt that the AGEP was related to daptomycin and considered that teicoplanin (TARGOCID) was the other causative factor.
11683282 Version 1)	86 yo/M/ France	MRSA endocarditis	3rd day	Daptomycin/ Cipro	700 mg q OD	Diagnostic information of drug eruption: AGEP was diagnosed at the department of dermatology (based on observation.
111690827/1172 8877 11739697 Version 1)/ 1685041/ 11691531 11749710 Version 2) Literature report: Momin SB, et al AGEP: an enigmatic drug-induced reaction	70 yo/M/ USA	Unknown	Unknown	Daptomycin/ Pip-tazo; Fluconazole; Levo; Vanco	Unknown	Outcome and causality of the events were not reported
118363743/ 11868836 11876048 1187865 Version 1)	75yo/M/ Brazil	Sepsis (off-label)	Day 6	Dapto; HCTZ; Atenolol Enalapril maleate; Resperidone/ atorvastatin; omeprazole; diltiazem HCl; phenytoin	750 mg qd	The patient fully recovered from skin exfoliation, erythema and rash pustular on an unknown date. Causality of the events was not reported.

Table3: Acute Generalized Exanthematous Pustulosis Cases Associated with Daptomycin (Continued)

Case Number	Age/Gender / Country	Indication	Onset of Skin Eruption	Suspect Medication(s)	Daptomycin Dose	Oucome/Causality Assessment
8418593 (Version1); 9275943 (Version 2) Literature report: Acute Generalized Exanthematous Pustulosis Caused by Daptomycin	57 yo/M/ Singapore	MRSA bacteremia	Unknown	Unknown	Unknown	Patient recovered. without sequel..
6034032 (V#2)	69 y/M/USA	MRSA bacteremia	Unknown	Dapto; other multiple meds	400 mg q 48h	Patient died of acute sepsis syndrome from disseminated MRSA infection, presumably from an initial pacemaker infection. assessed as secondary to sepsis
9367296 (Version 1)	80 yo/M/France	MRSE endocarditis	3rd day	Dapto and gentamicin sulfate	Unknown	Event was reported as possibly related to Cubicin and Gentalline (gentamicin sulfate). Pt was lost to follow-up.

Reviewer's Comment: Based on review of the new safety information regarding AGEP cases possibly associated with daptomycin use, the clinical reviewer recommends addition of this adverse reaction under the Postmarketing Experience subsection of the Daptomycin for Injection prescribing information.

4. Conclusion and Recommendation

From the clinical standpoint, this NDA is recommended for approval pending CMC review and completion of drug facilities inspection deficiencies.

5. Labeling Review

Based on review of the AGEP cases, the clinical reviewer has the following safety labeling recommendation (addition of "acute generalized exanthematous pustulosis" under the Post-marketing Experience subsection) for the RLD-Cubicin® (daptomycin for injection) and Sagent's Daptomycin for Injection prescribing information.

"6.2 Post-Marketing Experience

Skin and Subcutaneous Tissue Disorders: serious skin reactions, including Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement); acute generalized exanthematous pustulosis."

References:

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