NDA Summary Review

NDA #/Supplement #	213645/ S-001
Applicant	Baxter Healthcare
Date of Submission	April 29, 2022
PDUFA Goal Date	February 28, 2023
Proprietary Name / Established (USAN) names	Daptomycin in Sodium Chloride Injection
Dosage forms/Strength	350 mg/50 mL (7 mg/mL), 500 mg/50 mL (10 mg/mL), 700 mg/100 mL (7 mg/mL), and 1,000 mg/100 mL (10 mg/mL) in single-dose GALAXY Container
No new indications are proposed in this supplement. This NDA is approved for the following indications	For the treatment of: • Complicated skin and skin structure infections (cSSSI) in adult and pediatric (1 to 17 years of age) patients. • *Staphylococcus aureus* bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis. • *Staphylococcus aureus* bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age).
Regulatory Action:	Approval

1. Background

Daptomycin is a cyclic lipopeptide antibacterial drug. It is used in the treatment of infections caused by aerobic gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin includes gram-positive bacteria including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates). Its mechanism of action is through binding to components of the cell membrane of susceptible organisms and causes rapid depolarization, inhibiting intracellular synthesis of bacterial DNA, RNA, and protein.

The Applicant originally submitted NDA 213645 on June 30, 2020, as a 505(b)(2) application for daptomycin lyophilized powder for injection, 500 mg/vial, and this NDA received a Complete Response (CR) action on April 29, 2021, due to an inadequate safety qualification of leachables. Please see the Multidisciplinary NDA Summary Review signed into DARRTS dated April 29, 2021, for additional details related to the original submission.

The Applicant resubmitted the NDA on July 30, 2021. In this second cycle review the Applicant provided sufficient nonclinical information to address the deficiencies identified in toxicological risk assessments for the 5 unqualified leachables (b) (4) and NDA 213645 for Dapzura RT® (daptomycin for Injection), lyophilized powder containing 500 mg daptomycin per single-dose vial container, received an approval action on January 25, 2022.

On April 29, 2022, this efficacy supplement to NDA 213645 (S-001) was submitted for the addition of the premixed drug product Daptomycin in Sodium Chloride Injection,

frozen in GALAXY single-dose container closure [350 mg in 50 mL (7 mg/mL); 500 mg in 50 mL (10 mg/mL); 700 mg in 100 mL (7 mg/mL); 1,000 mg in 100 mL (10 mg/mL)] which is a change in formulation from the approved NDA 213645. The review and regulatory decision for this change in formulation is discussed within this review.

On October 17, 2022, the Applicant notified FDA that they did not plan on marketing Dapzura RT® due to lack of commercial interest.

2. Current Submission

The Applicant submitted this 505(b)(2) supplemental New Drug Application (sNDA) for Daptomycin in Sodium Chloride Injection in Galaxy container that relies on FDA's finding of safety and effectiveness for the listed drug (LD), Cubicin and Cubicin RF (daptomycin for injection) lyophilized powder 500 mg/vial, (NDA 021572), held by Cubist Pharmaceuticals LLC. There are no proposed changes to the indications, active ingredient, and route of administration when compared to the LD. The proposed drug product administration will be at the same dose/route and administration regimen as the LD, Cubicin by injection (4-6 mg/kg administered by IV infusion over a 30-minute period). However, for this sNDA there are differences in strength, formulation, and excipients.

Office of Product Quality (OPQ)

There are no changes to the daptomycin drug substance specification approved in the NDA; the acceptance criteria and the associated analytical methods remain the same as currently approved. The daptomycin drug substance manufacturer remains the same as currently approved in the NDA. The proposed drug product contains new excipients with respect to the LD and the currently approved powder formulation. The new product contains monobasic phosphate (b) (4) and dibasic sodium phosphate (b) (4) used as buffering agents. Mannitol and sorbitol, used as (b) (4) in the powder formulation, are not present in the currently proposed premixed solution formulation. Based on a survey of approved injectable products, the levels of inactive ingredients/excipients used in the proposed drug product are acceptable from a chemistry, manufacturing and controls (CMC) perspective. Furthermore, the Division of Biopharmaceutics (Biopharm) assessment concluded that the bridge between the proposed drug product/new presentation and LD formulations was adequately established. Refer to the Biopharm review, dated February 9, 2023, in Panorama for full details.

The proposed drug product's release and stability (shelf-life) specifications were appropriately established based on 1) test results of the reference products (Cubicin and Cubicin RF), 2) data from development studies conducted on the proposed formulation, 3) ICH Guidelines [Q6A, Q3B(R2), Q3C, and Q3D], and 4) USP requirements. Batch release results and stability data provided for six registration stability batches of Daptomycin in Sodium Chloride Injection in Galaxy container indicate that all batches met the acceptance criteria for all product quality attributes tested with batch-to-batch consistency. The stability data support the proposed expiration dating period of 12 months at frozen (at or below - 20°C) storage with a thawed label statement of 30 days under refrigeration (5°C/41°F) or 48 hours at room temperature (25°C/77°F).

All manufacturing facilities responsible for commercial production of the proposed drug product were approved by the Office of Pharmaceutical Manufacturing Assessment.

This supplemental application for the proposed Daptomycin in Sodium Chloride Injection in Galaxy container is recommended for approval from a CMC perspective. Refer to the CMC review, February 21, 2023, in Panorama for further details.

Pharmacology/Toxicology

The currently proposed drug product, Daptomycin Sodium Chloride Injection in Galaxy container, contains the excipients monobasic sodium phosphate and dibasic sodium phosphate not included in Baxter's approved Dapzura RT daptomycin for injection or in the LDs. These excipients (monobasic sodium phosphate and dibasic sodium phosphate) are found at higher levels in other FDA approved drugs that may be given by the intravenous route for the same duration of treatment (up to 6 weeks). There are no further nonclinical concerns for the use of monobasic and dibasic sodium phosphate at the proposed levels in the new drug product. The levels of impurities in Daptomycin Sodium Chloride Injection do not exceed levels of impurities in the LDs (Cubicin and Cubicin RF) and therefore, there are not concerning from a pharmacology/toxicology perspective for any drug-related impurities detected in the new drug product.

A leachables assessment and a toxicological risk assessment of several leachables detected in Daptomycin Sodium Chloride Injection in Galaxy container were provided by the Applicant in this sNDA. Several (b) (4) (8 in total) were detected in the leachables assessment, likely associated with the container closure system (GALAXY bag), that exceeded toxicological safety thresholds of concern (i.e., 5 mcg/day). The Applicant reasonably considered expected metabolites of the (b) (4) as surrogates to evaluate the potential risks of exposure to leachables to patient populations exposed to the (b) (4) in Daptomycin Sodium Chloride Injection. The toxicological risk assessment included adequate sources of toxicological and bioavailability information for the individual leachables to account for route-to-route extrapolations for toxicological studies conducted by routes of exposure other than the intended intravenous exposure to Daptomycin Sodium Chloride Injection. The leachables toxicological risk assessments and included Permissible Daily Exposure levels (PDEs) with reasonable exposure margins to the maximum potential leachable exposure to patients (all populations) administered Daptomycin Sodium Chloride Injection were considered adequate. Therefore, all of the detected (b) (4) leachables in Daptomycin Sodium Chloride Injection are unlikely to pose significant risks to humans and are considered qualified from a pharmacology/toxicology perspective. Refer to the Pharmacology/Toxicology Review for this sNDA in DARRTS (February 2, 2023) for a detailed review of the Applicant's toxicological risk assessments.

The labeling for Daptomycin Sodium Chloride Injection complies with the current Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) content and formatting and there are no pharmacology/toxicology changes to the labeling.

Clinical Pharmacology and Labeling

No new clinical pharmacology studies were conducted for this NDA. The recommended dosage and administration regimens for the proposed Daptomycin in Sodium Chloride in GALAXY Container are the same as that of CUBICIN (i.e., the listed drug).

Due to differences in the dosage form of the two products (i.e., the listed drug is a lyophilized powder for reconstitution while the proposed product is a single-dose premixed bag with a set volume of either 50 mL or 100 mL), the Applicant proposed revisions to SECTION 2 DOSAGE AND ADMINISTRATION. The clinical pharmacology review team reviewed the proposed revisions and provided recommendations for SECTION 2 DOSAGE AND ADMINISTRATION Subsections 2.1, 2.3, 2.5 and 2.7, and SECTION 8 USE IN SPECIFIC POPULATIONS Subsection 8.4 to reflect the unique administration requirements and limitations of use for the proposed product. The Applicant has agreed to adopt the review team's recommendations. Refer to Table 1 for a summary of the clinical pharmacology-related changes to the prescribing information (PI) submitted on April 29, 2022.

Table 1. Summary of High-level Labeling Changes to the Clinical Pharmacology Information in the PI

Summary of Labeling Changes		
Section/Subsection of the PI	**Applicant's Proposed Labeling**	**FDA Recommended Labeling Change**
HIGHLIGHTS of the PI	Information recommended by FDA in the next column was not originally included in the Applicant's proposed labeling.	Updated with administration information regarding the limitations of the GALAXY container added to the Dosage and Administration sections of the FPI. Refer to comments below.
2 DOSAGE AND ADMINISTRATION Subsections 2.1, 2.3 and 2.5	Did not include limitation of use for single-dose GALAXY container.	In Subsections 2.1, 2.3 and 2.5, addition of: "If a dose of Daptomycin in Sodium Chloride Injection is required that does not equal 350 mg, 500 mg, 700 mg or 1,000 mg, this product is not recommended for use and an alternative formulation of daptomycin should be considered"
8 USE IN SPECIFIC POPULATIONS Subsection 8.4	Information recommended by FDA in the next column was not originally included	In Subsection 8.4, addition of: "Because of the limitations of the available

	in the Applicant's proposed labeling.	strengths and administration requirements (i.e., administration of fractional doses is not recommended) of Daptomycin in Sodium Chloride Injection, and to avoid unintentional overdose, this product is not recommended for use if a dose of Daptomycin in Sodium Chloride Injection is required that does not equal 350 mg, 500 mg, 700 mg or 1,000 mg and an alternative formulation of daptomycin should be considered *[see Dosage and Administration (2.3, 2.5)]."*
Reviewer's comment: The recommended addition was to prevent medication errors due to fractional dosing with the single-dose GALAXY container(s).		
2 DOSAGE AND ADMINISTRATION Subsection 2.7	Removed (b) (4) [redacted]	Addition of, "*For Intravenous infusion over a period of 60 minutes in pediatric patients 1 to 6 years of age*: The infusion rate should be maintained at 0.83 mL/min for a 50 mL galaxy container and 1.67 mL/min for a 100 mL galaxy container at 0.42 mL/minute over the 60-minute period. *For Intravenous infusion over a period of 30 minutes in pediatric patients 7 to 17 years of age*: The infusion rate should be maintained at 1.67 mL/min for a 50 mL galaxy container and 3.33 mL/min for a 100 mL galaxy

		container over the 30-minute period."

Reviewer's comments: FDA did not agree with the Applicant's original proposal to: (1) [redacted] (b) (4)

[redacted] (b) (4) *Therefore, as addressed under the FDA recommended labeling changes for Subsections 2.3, 2.5 and 8.4, we have recommended limiting use of the premixed bags to patients requiring doses equivalent to the proposed dose strengths and specified the appropriate infusion rate limits for the corresponding galaxy containers.*

The Applicant has implemented the changes proposed by FDA.

Clinical and Labeling

No new clinical studies were conducted for this sNDA. A comprehensive safety review of daptomycin from published literature, case reports, and FDA Adverse Event Reporting System (FAERS) since the approval of Dapzura RT was submitted on July 12, 2022 (SDN 36). There were no new safety signals identified.

Removal of Hereditary Fructose Intolerance Information from Labeling

Dapzura RT contained [redacted] (b) (4) sorbitol as an excipient. Sorbitol may precipitate a metabolic crisis in patients with Hereditary Fructose Intolerance (HFI). Therefore, there was a **CONTRAINDICATION** listed in Section 4 for patients with known or suspected HFI. Also, a **WARNING AND PRECAUTION** regarding risk in patients with HFI was listed in subsection 5.11 in the **Pediatric Use** subsection (subsection 8.4) and **PATIENT COUNSELING INFORMATION** (section 17) of the PI. The proposed formulation of Daptomycin in Sodium Chloride Injection does not contain sorbitol, and Dapzura RT will no longer be marketed, so this contraindication and warning were removed from the PI.

Impact of Monobasic and Dibasic Sodium Phosphate as Buffers and Hydrochloric Acid as a pH Adjuster

Daptomycin in Sodium Chloride Injection contains monobasic and dibasic sodium phosphate as buffers and hydrochloric acid as a pH adjuster which are not contained in the LD. The maximum daily intake (MDI) of 50 mg for Monobasic Sodium Phosphate, [redacted] (b) (4) associated with the new product is above the maximum daily exposure (MDE) reported in the FDA Inactive Ingredients Database (IID) (40 mg) for FDA approved IV injectables. [redacted] (b) (4) .

The Applicant performed a comprehensive evaluation of clinical and non-clinical literature to assess whether the excipients monobasic and dibasic sodium phosphate and hydrochloric acid impact the in vivo physiological disposition of daptomycin in human subjects. No data were found indicating monobasic and dibasic sodium phosphate and hydrochloric acid would impact daptomycin disposition in humans. The Applicant referred (b) (4)

(b) (4) Overall, the difference in formulation is not expected to change the in vivo disposition of daptomycin.

Labeling to Address Limitations of the GALAXY Container

Daptomycin in Sodium Chloride Injection is a premixed formulation in GALAXY container, which should not be used for fractional dosing. On July 1, 2022, the Division sent an information request (IR) to include language in the PI stating a limitation of use imposed by the available strengths of the premixed product and a recommendation against fractional dosing for this formulation. The Applicant added a statement (SDN 35) in sections 2.3 (Dosage in Pediatric Patients (1 to 17 Years of Age) for cSSSI), 2.5 (Dosage in Pediatric Patients (1 to 17 Years of Age) with *Staphylococcus aureus* Bloodstream Infections (Bacteremia)), and 8.4 (Pediatric Use). Per the Division's recommendation, this statement was also added to the Dosage and Administration sections within the HIGHLIGHTS OF PRESCRIBING INFORMATION and in Section 2.1 (Important Administration Duration Instructions). Please refer to the Clinical Pharmacology and Labeling section of this review for additional information.

(b) (4)

(b) (4)

(b) (4). The Applicant refers to the LD which has been approved for use in pediatric patients 1 to 17 years of age. Also, the Applicant provided a summary of the literature describing the use of daptomycin in over 1,500 pediatric patients. Safety and efficacy findings from this literature are consistent with the information in the labeling of the LD.

(b) (4)

3. Regulatory Action

This supplemental NDA for Daptomycin in Sodium Chloride Injection, 350 mg/50 mL (7 mg/mL), 500 mg/50 mL (10 mg/mL), 700 mg/100 mL (7 mg/mL), and 1,000 mg/100 mL (10 mg/mL) in single-dose GALAXY Container, will receive an approval action.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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