# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209949Orig1s000

# SUMMARY REVIEW

# Combined Cross-Discipline Team Leader and Division Director Review

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Dorota Matecka, PhD; Sumathi Nambiar MD MPH |
| **Subject** | Cross-Discipline Team Leader and Division Director Review |
| **NDA #** | 209949 |
| **Applicant** | Xellia Pharmaceuticals ApS |
| **Date of Submission** | December 20, 2016 |
| **PDUFA Goal Date** | October 20, 2017 |
| **Proprietary Name / Established (USAN) names** | Daptomycin for Injection* (daptomycin) |
| **Dosage forms/Strength** | Powder for injection, 350 mg/vial |
| **Proposed Indication(s)** | For the following indications in adults:<br>1. Complicated skin and skin structure infections<br>2. *Staphylococcus aureus* bloodstream infections (including those with right-sided infective endocarditis) |
| **Regulatory Action:** | Approval |

** No proprietary/trade name was proposed for the drug product*

| **Material Reviewed/Consulted** Action Package including: | **Names of Discipline Reviewers** |
|---|---|
| Pharmacology Toxicology Review | Terry Miller PhD |
| Product Quality Application Technical Lead | Dorota Matecka PhD |
| Medical Officer Review | Alma Davidson MD |
| Clinical Microbiology Review | Avery Goodwin PhD |
| Clinical Pharmacology Review | Sonia Pahwa PhD |
| Office of Prescription Drug Promotion (OPDP) Review | Puja Shah PharmD |
| Division of Medication Errors Prevention and Analysis (DMPA) Review | Sevan Kolejian PharmD |

## 1. Introduction

This 505(b)(2) NDA submitted by Xellia Pharmaceuticals ApS (Xellia) provides for a new vial size (strength) of daptomycin lyophilized powder for intravenous administration to be used for the treatment of the same indications provided in the labeling of the listed drug (LD), Cubicin® (daptomycin for injection), 500 mg/vial, approved via NDA 21572 and marketed by Cubist Pharmaceuticals, Inc. Due to the difference in the total vial content (strength) of daptomycin (350 mg/vial for the proposed product versus 500 mg/vial for Cubicin), this NDA was submitted under 505(b)(2) and not under a 505(j). Although another 505(b)(2) NDA was recently approved for daptomycin for injection, 350 mg (NDA 208385 held by Sagent Pharmaceuticals, Inc.), the current NDA still qualifies as a 505(b)(2) NDA since it had been

submitted on December 20, 2016, which is prior to the approval date of NDA 208385 (September 12, 2017).

The proposed drug product has the same active ingredient, excipients, (b) (4) route of administration, dosage form and indications as Cubicin. The only difference between the two products is the strength (i.e., the amount of daptomycin per vial) with the Cubicin product and the drug product proposed via this NDA containing 500 mg and 350 mg of daptomycin per vial, respectively. However, the concentration of the solution following reconstitution with 0.9% sodium chloride will be the same for the proposed drug product and the LD (i.e., 50 mg/mL). In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on the Agency's previous findings of effectiveness and safety for Cubicin for approval of the proposed drug product.

## 2. Background

Daptomycin is a cyclic lipopeptide antibacterial drug which acts by binding to bacterial membranes and causing a rapid depolarization of the membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death. Daptomycin for injection, which was originally approved in 2003 under NDA 21572 [Cubicin (daptomycin for injection), 500 mg/vial], is indicated for the treatment of complicated skin and skin structure infections and *Staphylococcus aureus* bloodstream infections (including those with right-sided infective endocarditis).

## 3. Product Quality

The Product Quality Team from the Office of Pharmaceutical Quality (OPQ) included the following individuals:

| DISCIPLINE | PRIMARY REVIEWER | SECONDARY REVIEWER |
|---|---|---|
| Drug Substance | Haripada Sarker | Benjamin Stevens |
| Drug Product | Milton Sloan | Balajee Shanmugam |
| Process | Ying Wang | Upinder Atwal |
| Microbiology | Yuansha Chen | Neal Sweeney |
| Facilities | Frank Wackes | Christina Capacci-Daniel |
| Biopharmaceutics | Gerlie Gieser | Elsbeth Chikhale |

The chemistry manufacturing and controls information for daptomycin drug substance has been provided via a reference to DMF Type II 27179 held by Xellia Pharmaceuticals Ltd., Hungary. The Drug Substance Reviewer, Dr. Haripada Sarker, noted that DMF 27179 has been found to be adequate via a chemistry review referenced for another application. The retest period for daptomycin established by the drug substance manufacturer is (b) (4). However, the retest period established by the current drug product manufacturer (b) (4) for daptomycin drug substance is (b) (4).

Daptomycin for Injection, 350 mg/vial, is a pale yellow to light brown lyophilized powder, which does not contain any excipients other than sodium hydroxide used as a pH adjusting agent. The proposed drug product is intended to be a copy of the listed drug, Cubicin, with the same active ingredient, excipients, (b) (4), route of administration, dosage form and indications. The only difference between the two products is strength, i.e., the total content of daptomycin per vial; Cubicin contains 500 mg daptomycin per vial whereas the drug product proposed via this NDA contains 350 mg of daptomycin per vial. However, the concentration of the solutions following reconstitution with 0.9% sodium chloride is the same for the proposed drug product and the listed drug (i.e., 50 mg/mL). The Applicant requested a waiver of the bioequivalence (BE) requirement in accordance with 21 CFR § 320.22(b)(1). Based on the information provided in the NDA, including comparable pH and osmolality results for the reconstituted solutions of the currently proposed drug product and the listed drug, the biowaiver request has been found acceptable by Dr. Gieser.

The drug product specification, which contains a number of attributes relevant for the proposed dosage form, including controls for impurities/degradation products, was found adequate. The analytical procedures have been described in reasonable detail and the validation reports have been found adequate. The container-closure system, which is the same as the container closure system used for another product, daptomycin for injection, 500 mg (b) (4) clear glass vials with 20 mm rubber stopper and aluminum seal with flip off cap. Based on the overall stability information provided in the NDA that includes up to 36 months of long-term (5°C ± 3°C) and 6-month accelerated (25°C ± 2°C/60% RH ± 5% RH) stability data for three representative stability batches, the proposed expiration dating period of 36 months for the proposed drug product stored at (b) (4) was found acceptable by Dr. Milton Sloan. In addition, the results of in-use stability studies (conducted using freshly manufactured and aged drug product samples) were found to be adequate to support the storage statements for the reconstituted and further diluted solutions of the drug product proposed in the package insert.

The manufacturing process consist of the following (b) (4) in a drug product vial was found acceptable by Dr. Wang.

No deficiencies for the proposed drug product were identified from the product quality microbiology perspective. During the NDA review several comments were forwarded to the Applicant and additional information was provided, such a (b) (4) the finished drug product. The overall product quality microbiology information provided for the drug product in the NDA was found acceptable by Dr. Chen.

The daptomycin drug substance manufacturer is Xellia Pharmaceuticals Ltd, Hungry and the drug product manufacturer is Gland Pharmaceuticals, USA. In addition, two other facilities (Xellia Pharmaceuticals ApS, Denmark and (b) (4)

(b) (4)) are involved in the microbiological testing of the drug substance. Based on the review of the application and inspectional history for all manufacturing and testing sites listed in this NDA, the overall recommendation of "Approve" was entered into Panorama for this NDA by the Office of Process and Facilities on September 26, 2017.

Based on the above assessments and the overall acceptable recommendation for facilities, this NDA is recommended for approval from the Product Quality perspective (review dated October 4, 2017 in Panorama).

## 4. Nonclinical Pharmacology/Toxicology

Dr. Terry Miller, the Pharmacology/Toxicology Reviewer, stated that the Applicant did not submit any new pharmacology/toxicology information in this NDA. Dr. Miller also stated that the Applicant's proposed language for the pharmacology/toxicology relevant sections of the labeling, are consistent with the latest drug product labeling for the listed drug, Cubicin. Dr. Miller recommends approval for this NDA (review dated September 5, 2017 in DARRTS).

## 5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Sonia Pahwa, stated that since no new clinical pharmacology data were submitted by the Applicant in this NDA, the clinical pharmacology team has no additional comments on this submission other than labeling comments (review dated August 24, 2017 in DARRTS).

## 6. Clinical Microbiology

The Clinical Microbiology Reviewer, Dr. Avery Goodwin, stated that the proposed microbiology section of the labeling is consistent with the labeling of the listed drug and recommends approval of this NDA from a clinical microbiology perspective (review dated August 31, 2106 in DARRTS).

## 7. Clinical/Statistical – Efficacy and Safety

Dr. Alma Davidson was the Clinical Reviewer for this NDA.

Dr. Davidson states that there are no clinical trials conducted by the Applicant to support this NDA and that the NDA relies on FDA's prior determination of effectiveness and safety of daptomycin based on studies.

Dr. Davidson further notes that the review of the literature identified no new safety information. The most frequently reported adverse events are gastrointestinal disorders,

infections and infestations, musculoskeletal and connective tissue disorder, nervous system disorders, and skin and subcutaneous tissue disorders.

Dr. Davidson recommends this NDA for approval. In addition, Dr. Davidson also recommends revisions to the proposed labeling to align with the Cubicin labeling (refer to review dated August 24, 2017 in DARRTS).

## 8. Advisory Committee Meeting

This NDA was not discussed at an advisory committee meeting as there were no specific questions that needed input from the committee.

## 9. Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

## 10. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

The listed drug, Cubicin (daptomycin for injection), 500 mg/vial, had several pending patents listed in the Orange Book at the time NDA 209949 was submitted. There is only one unexpired patent listed for Cubicin in the Orange Book at this time:

- US Patent No. 8,003,673 - Expiry Date: September 4, 2028

Xellia has submitted Paragraph IV certifications regarding the above patents and notified the patents and the NDA holders (Merck and Co., Inc., Cubist Pharmaceuticals Inc., and Cubist Pharmaceuticals, LLC) on February 22, 2017, that they had submitted an NDA to the FDA under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Subsequently, on July 14, 2017, Xellia notified the FDA that no litigation has been initiated within the 45 day period following receipt of the notice.

# 11. Labeling

No trade name was proposed for the drug product. Labeling revisions and recommendations were provided from several disciplines including DMEPA and OPDP. All recommended changes were agreed to and incorporated by the Applicant in the package insert, and the respective carton and container labels. With the passage of the FDA Reauthorization Act (FDARA) on August 18, 2017, FDA was given the authority to include a disclaimer statement in product labels for 505(b)(2) applications where protected pediatric information is removed and statements of appropriate pediatric information necessary to assure safe use (see amended section 505A(o) of the Federal Food, Drug & Cosmetic Act). The disclaimer statements were added to the proposed labeling. A final agreed to label will be appended to the action letter.

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SUMATHI NAMBIAR
10/19/2017