CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202106Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202106
Applicant	B. Braun Medical, Inc.
Date of Submission	October 30, 2014 (*Class 2 NDA Resubmission*)
PDUFA Goal Date	April 30, 2015
Proprietary Name / Established (USAN) names	Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex Container
Dosage forms/Strength	500 mg of meropenem for injection and 50 mL sodium chloride 1 g of meropenem for injection and 50 mL sodium chloride
Proposed Indication(s)	Complicated skin and skin structure infections Complicated Intra-abdominal Infections Bacterial Meningitis
Recommended:	Approval

1. Introduction

This 505(b)(2) NDA submitted by B. Braun Medical, Inc. provides for Meropenem for Injection USP and Sodium Chloride Injection USP packaged in the Duplex® Container (packaging system manufactured by B. Braun). The listed drug (LD) for this NDA is Merrem® IV (500 mg/vial and 1 g/vial strengths) approved via NDA 50706 for Astra Zeneca.

There is no IND associated with the application and no clinical data have been submitted. The applicant is relying on previous findings of efficacy and safety for Merrem® IV for approval of the current product. The majority of the information submitted in the original NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed drug product. In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant on the basis of 21 CFR 320.22 (b): "a drug product's in vivo bioavailability or bioequivalence may be considered self-evident".

This NDA, originally submitted on September 27, 2013, was issued a complete response (CR) letter on July 25, 2014. The only deficiency identified in the CR letter was an unacceptable status of the proposed drug product manufacturing facility (Facta Farmaceutici S.p.A., Teramo, Italy). In addition to addressing this deficiency, the applicant was requested to include in the NDA resubmission a proposed drug product labeling and the safety update. Since most of the reviewers found this NDA acceptable in the first review cycle, for details regarding this application please refer to the original NDA reviews and the first CDTL review dated July 5, 2014. The current review covers only the reviews of the applicant's response to the deficiencies and comments outlined in the CR letter.

2. Background

Meropenem is a synthetic, carbapenem antibacterial drug for intravenous administration. The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa*; and PBPs 1, 2 and 4 of *Staphylococcus aureus.*

Merrem® IV (meropenem for injection) 500 mg/vial and 1 g/vial was approved via NDA 50706 in 1996. There are several generic formulations of meropenem IV approved for use in humans in the US. As discussed above, the active ingredient, strength, dosage form, and route of administration are the same between the drug product proposed by B. Braun Medical, Inc. and the listed drug, Merrem® IV. The B.Braun product differs from the LD in that only the diluent (Sodium Chloride Injection, 0.9%) supplied with meropenem in the proposed packaging system (Duplex® Container) can be used, whereas Merrem® IV can be used with a number of commercially available diluents shown to be compatible with Meropenem for Injection (as listed in the Merrem® IV labeling).

The Duplex® Container is a flexible dual chamber container designed to maintain the integrity of the contents of the drug chamber and diluent chamber during shipping and storage while maintaining them in a ready-to-use (RTU) configuration without the need for freezing/thawing or any other special storage conditions. In addition, the Duplex® Container is designed to allow the user to reconstitute the drug and diluent without the use of metal needles or a laminar flow hood.

There are several drug products currently approved and marketed in the United States in the Duplex® Container system. They include the following products:

• Cefazolin for Injection USP and Dextrose for Injection USP in the Duplex® Container (NDA 50779)
• Cefuroxime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50780)
• Cefotaxime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50792)
• Ceftriaxone for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50796)
• Cefoxitin for Injection USP and Dextrose Injection USP in the Duplex® Container (ANDA 65214)
• Cefotetan for Injection USP and Dextrose Injection USP in the Duplex® Container (ANDA 65430)
• Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50821)
• Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50823)

3. Product Quality

The Product Quality Microbiology Reviewer was Vinayak B. Pawar, Ph.D who recommended this NDA for approval from the product quality microbiology standpoint in the first review cycle (review dated June 30, 2014 in DARRTS).

The CMC Reviewer was Lin Qi, Ph.D., who in the first review cycle recommended a non-approval based on an unacceptable status of the drug product manufacturing facility, Facta Farmaceutici S.p.A., in Teramo, Italy and the Overall "Withhold" Recommendation received from the Office of Compliance (for details refer to the review dated June 20, 2014 in DARRTS). With the NDA resubmission, however, the drug product facility issues were resolved satisfactorily and the Overall Manufacturing Inspection Recommendation issued by the Office of Process and Facilities for this NDA is now "Acceptable". In addition, as recommended by the Agency, the (b) (4) was replaced with "Duplex Container" in the currently proposed labeling, and the labeling and labels were found acceptable by Dr. Qi from the CMC perspective. Therefore, as all outstanding product quality issues have been now resolved, Dr. Qi recommends this NDA for approval from the Product Quality perspective (review dated April 29, 2015, in Panorama).

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Ellis Ph.D. was the Pharmacology/Toxicology Reviewer for this application and concluded in the first review cycle that from the nonclinical pharmacology standpoint, the NDA can be approved (for details refer to the review dated May 22, 2014 in DARRTS). Since no new pharmacology/toxicology information was submitted in this NDA resubmission, no new review was performed.

5. Clinical Pharmacology/Biopharmaceutics

Elsbeth Chikhale, Ph.D., was the Biopharmaceutics Reviewer of this NDA and recommended it for approval from the biopharmaceutics perspective in the first review cycle (review dated June 2, 2014 in DARRTS). No new review was conducted for this NDA resubmission.

The Clinical Pharmacology Reviewer, Dr. Ryan Owen, stated that application is acceptable from a clinical pharmacology perspective as no new clinical pharmacology information was submitted by the applicant in this NDA. In addition, Dr. Owen stated in his review that the proposed labeling changes in the sections relevant for clinical pharmacology have been found acceptable (review dated March 13, 2015 in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D., was the Clinical Microbiology Reviewer for this application (refer to the first cycle review dated May 14, 2014 in DARRTS). No new clinical

microbiology information was submitted and no new review was filed for this NDA resubmission.

7. Clinical Efficacy/Safety

Alma Davidson, MD, was the Clinical Reviewer for this NDA. Applicant is relying on the FDA prior determination of efficacy and safety of the listed drug and this 505(b)(2) NDA and does not contain any clinical studies. Therefore, Dr. Davidson's latest review (dated April 27, 2015) focused on the safety update submitted in the NDA resubmission. The Applicant performed a search of the medical and scientific literature for the time period from December 1, 2013 through July 31, 2014. This search was intended to identify any significant changes or findings in the safety profile of meropenem including new adverse events or changes in frequency of known adverse events since the last meropenem package insert update.

Based on review of the safety information, several adverse reactions were identified, e.g., one CNS adverse reaction, delirium associated with meropenem was identified in a patient who received meropenem for treatment of UTI and urosepsis. In addition, hypomagnesemia and increased GGT were identified as new adverse laboratory reactions in a clinical trial publication. Dr. Davidson stated that FDA will continue to monitor these adverse reactions from the LD core data reports but no labeling changes are warranted at this time. Dr. Davidson did recommend several other labeling revisions. That includes revisions to several sections of the package insert to address the high sodium content of this product. Dr. Davidson stated that the proposed labeling for the current product will be revised accordingly upon receipt of the revised labeling for the listed drug (Merrem® IV) to reconcile the two package inserts.

In conclusion, Dr. Davidson recommends this application for approval (for details refer to the review dated April 27, 2015 in DARRTS). Margaret Gamalo, Ph.D., was the Statistical Reviewer for this NDA. No new statistical review was filed for this NDA resubmission.

8. Advisory Committee Meeting

There was no Advisory Committee Meeting for this 505(b)(2) application.

9. Pediatrics

The Applicant requested a full waiver of the requirement to submit pediatric assessments in connection with this NDA. Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container is a single use container designed to deliver 500 mg or 1 gram of meropenem and is not appropriate for use in children who do not require the full doses because of safety issues related to potential overdose. The Dosage and Administration section of the proposed product labeling informs the clinician not to use this product for pediatric patients requiring less than the full dose.

It should be noted that the drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application.

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). There are no other relevant regulatory issues for this application.

11. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed package insert and the container and carton labels submitted in the original NDA and provided several recommendations (review in DARRTS dated June 10, 2014). As requested by the Agency in the CR letter, the proposed revised product labeling and labels have been provided in the NDA resubmission. DMEPA has reviewed the updated labeling documents and issued a recommendation "to revise one of the colors on the container of either the 500 mg or the 1g strength by choosing a color other than (b) (4) to mitigate wrong strength selection errors."

All changes recommended by the team were included in the package insert, and the container labels.

12. Recommendations/Risk Benefit Assessment

Several injectable formulations of meropenem have been marketed in the US since approval of the LD, Merrem® IV (meropenem for injection), in 1996 via NDA 50706. The proposed drug product via this 505(2) NDA, Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex Container, would provide an alternative product that would have the risk-benefit profile similar to the LD; however, it is designed to allow the user to reconstitute the drug without the use of metal needles or a laminar flow hood. There are no unresolved issues or deficiencies that need to be conveyed to the sponsor. No PMRs, PMCs, or pediatric studies need to be requested.

The overall recommendation for this NDA should be Approval. This conclusion is based on recommendations from all Disciplines involved in the review of this application.

Dorota M. Matecka -S

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