CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202106Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure Review

Application Number: 202106

Submission Date(s): October 30, 2014

Applicant: B. Braun Medical, Inc.

Product: Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container

Reviewer: Alma Davidson, M.D.

Date of Review: April 27, 2015

Covered Clinical Study (Name and/or Number): No new clinical studies were conducted for this application. Therefore, no financial disclosure information is necessary.

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from applicant)
Total number of investigators identified:		
Number of investigators who are sponsor employees (including both full-time and part-time employees):		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

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/s/

ALMA C DAVIDSON
04/29/2015

HALA H SHAMSUDDIN
04/29/2015

Clinical Review

NDA 202106	505(b)(2)
Date of Resubmission	October 30, 2014
New PDUFA Goal Date	April 30, 2015
Applicant	B. Braun Medical, Inc.
Drug Name	Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container
Dosage Forms/Strengths	500 mg of meropenem for injection and 50 mL sodium chloride 1 g of meropenem for injection and 50 mL sodium chloride
Proposed Indications	Complicated Skin and Skin Structure Infections Complicated Intra-abdominal Infections Bacterial Meningitis
Clinical Reviewer	Alma Davidson, M.D.
Medical Team Leader	Hala Shamsuddin, M.D.

1. Introduction

Meropenem is a synthetic, broad-spectrum, carbapenem antibacterial for intravenous administration. B. Braun Medical, Inc. has submitted a 505(b)(2) New Drug Application (NDA) 202106 for Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container to the FDA on September 27, 2013. In that submission, the Applicant received a Complete Response (CR) letter from the FDA, dated July 15, 2014. The following issues were identified in the letter: 1) Deficiencies in the manufacturing facility (Facta Farmaceutici S.p.A., in Teramo, Italy) inspection; 2) Updated proposed labeling; and 3) Safety update requesting information as described in 21 CFR 314.50 (d)(5)(vi)(*b*).The safety update should include data from all nonclinical and clinical studies/trials of the drug regardless of indication, dosage form or dose level.

In response to the CR letter, the Applicant sent a resubmission of NDA 202106 on October 30, 2014. The subject of this clinical review is the review of the submitted safety information and the reviewer's proposed labeling changes to the Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container package insert.

2. Background

B. Braun Medical-Meropenem has the same active ingredient and formulation, but is provided in a duplex container compared to the reference listed drug (RLD), MERREM® I.V. (meropenem for Injection) which is supplied in a glass vial. The B. Braun product differs from the RLD in that only the diluent (Sodium Chloride Injection, 0.9%) supplied with meropenem in the Duplex container can be used, whereas the RLD, Merrem® IV can be used with a number of commercially available diluents shown to be compatible with meropenem for injection (as listed

in the RLD label). The Applicant solely relied upon the Merrem® application, and did not include separate safety section in the application.

On February 13. 2015, the FDA communicated through electronic mail with the applicant regarding the following recommendation for revision of color used on the container label:

"Revise one of the colors used on the container of either the 500 mg or the l g strength by choosing a color other than (b) (4) to mitigate wrong strength selection errors. As presented, the colors are too close in hue and do not provide adequate differentiation between strengths."

On March 27, 2015, the FDA sent an electronic mail request to the applicant regarding our proposed revised labeling.

On April 10, 2015, the applicant submitted the labeling amendment in response to the FDA's email request for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container label. This amendment includes the revised container label and modified package insert to comply with the FDA's revised labeling request.

On April 23, 2015, the Division was notified from the Office of Compliance that the manufacturing site: FACTA FARMACEUTICI S.p.A (FACTA), Teramo, Italy re-inspection is found to be acceptable.

3. Safety Review

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. One hundred forty-one abstracts were identified referring to meropenem, of which 21 were considered possibly relevant to identifying new safety issues. Upon further review, 19 of these articles contained pertinent safety information.

Literature review

a) Reported adverse events

• Delirium was reported by Munoz-Gomez et.al in this case report. The authors describe the case of a 100-year-old man who received an initial 1 g I.V. dose of meropenem followed by 500 mg I.V. every 12 hours for a urinary tract infection. Two days after starting meropenem he became confused and agitated. A review of his medications showed that his only new medication was meropenem. Meropenem was discontinued and by the next day the patient was alert, oriented and no longer agitated. A month later he was readmitted with urosepsis caused by *Pseudomonas aeruginosa* resistant to piperacillin-tazobactam and again given meropenem. By the third day of

treatment he again became confused, and one day after discontinuing the meropenem his mental status returned to normal.

Clinical Comment: This patient experienced delirium after 2-3 days of meropenem therapy for UTI and urosepsis (off-label use). Dechallenge and re-challenge with meropenem was positive in this case which signals the central nervous system (CNS) effects of meropenem. Delirium is a labeled adverse reaction under Adverse Reactions-Systemic Adverse Reactions (Nervous System) subsection of the RLD label.

- A multicenter, double-blind, randomized phase II trial conducted by Lucasti et al assessed the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Of the 39 patients treated with meropenem I.V. (1 g every 8h), 2 (5.1%) showed hypomagnesemia, and 2 (5.1%) showed elevated gamma-glutamyl transferase (GGT) activity.

Clinical Comment: In this comparative trial, hypomagnesemia and increased GGT occurred equally in both treatment groups (ceftolozane-tazobactam plus metronidazole versus meropenem). Currently these two adverse laboratory reactions are not labeled in the Merrem package insert, however, the FDA will continue to monitor these events. No labeling changes are warranted at this time.

b) Possible increased percentage of labeled adverse reactions

- The same Lucasti trial also reported that both nausea and pyrexia were experienced by 10.3% of their 39 patients. This compares with the 0.1- 3.6% incidence rate for nausea and less than 1% incidence rate for pyrexia reported in the current Merrem® package insert.

Clinical Comment: In this same comparative trial, it is reported that both nausea and pyrexia were experienced in both treatment groups. Currently these two adverse reactions are labeled in the RLD package insert; however, the FDA will continue to monitor these adverse reactions. This possible increased percentage of labeled adverse reactions does not warrant a labeling change at this time.

- Wand X et. al. conducted a nine-center, randomized controlled clinical trial compared efficacy and safety of meropenem and biapenem.in the treatment of bacterial lower respiratory tract infections and urinary tract infections (UTls).The rate of drug-related adverse reactions for meropenem was 15.44% (21/136), most of which were mild and transient, with no observed serious adverse reactions. Reported laboratory abnormalities included increased serum

transaminases and decreased white blood cell count, (11.03% in the meropenem group). The package insert reported these adverse laboratory changes as "greater than the most recent Merrem® label group). The package insert reported these adverse laboratory changes as "greater than 0.2%.

• Yagi et al evaluated the incidence of liver dysfunction, renal dysfunction, and convulsions resulting from meropenem treatment. They stratified patients by renal function, and evaluated the effect of pharmacist intervention on outcome. The incidence of convulsions varied from 0.59 to 2.06 %, the incidence of renal dysfunction varied from 7.6 to 17.5 %, and the incidence of liver dysfunction varied from 11.1 to 28.9 %, all of these values being higher than the present package insert for Merrem.

• Hornik et al conducted a retrospective cohort study of 5,566 infants treated with meropenem or imipenem/cilastatin during their first 120 days of life in neonatal intensive care units between 1997 and 2010. They found that the incidence of death, as well as the combined outcome of death or seizure, was lower with meropenem use; meropenem was associated with more frequent but less severe adverse events, mainly laboratory adverse reactions, when compared with imipenem/cilastatin. Of the 3,479 infants in this study exposed to meropenem, 6.9% had an elevation of their aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

c) Use of meropenem in treatment of nervous system disease

Merrem® is FDA-approved for treatment of bacterial meningitis in pediatric patients equal or greater than 3 months in age. The package insert includes warnings that the incidence of seizures noted during clinical investigations in patients treated for non-CNS infections was 0.7%.

• An abstract by Wu et al describes an observational retrospective study on the incidence of seizures among neurosurgical patients treated with either meropenem of imipenem/cilastatin. There were 92 patients treated with meropenem over the course of a year, of which four were diagnosed with epilepsy before treatment and two (2.17%) were diagnosed during treatment. The authors concluded that "despite many other epileptogenic factors, imipenem or meropenem did not increase the risk of seizures in neurosurgical patients. There was not further risk for patients with pre-existing seizures or creatinine clearance abnormalities when dosed appropriate."

• Morita et al conducted an open-label study to evaluate the pharmacodynamics, clinical efficacy, and safety of meropenem for adult bacterial meningitis in Japan. Meropenem IV (2 g every 8 hours) was administered to five adults (aged 35-71). Eleven clinical and laboratory adverse events considered to be related to meropenem were reported.

These included liver dysfunction in four patients, oral candidiasis in one patient, skin rash in one patient, inflammation at the injection site in one patient, and transient rise in alkaline phosphatase in one patient, all of which are labeled and nonserious events; and one patient with transient rise of urinary protein level. The liver dysfunction in three of four patients and skin rash

in one patient were moderate, and all other reactions were termed as mild. There were no serious adverse events, no seizures reported and no discontinuation of treatment due to any adverse event.

d) Off-label dosage administration of meropenem

• Enriquez et al report the case of a 54-year-old man whose multiple brain actinomycotic abscesses were successfully treated with surgery and off-label meropenem (unknown dosage) for a total of 12 weeks, resulting in a complete neurological recovery and total resolution of the abscesses on MRI. No adverse reactions were reported.

• Manning et al retrospectively reviewed the clinical efficacy and safety of continuous infusions of meropenem in two Australian tertiary hospitals' outpatient parenteral antimicrobial therapy settings over a six year period. The patients had a range of infections, including lower respiratory tract (17), bone and joint (14), intra-abdominal (6), diabetic foot (4), urinary tract (3), otitis externa (2), and other (4). The patients received meropenem of dyspnea, neutropenia, or toxicity due to concomitant voriconazole. Asymptomatic thrombocytopenia and eosinophilia were observed in 2 (4%) and 4 (8%) patients, respectively, and two developed anemia during therapy. Elevated ALT occurred in 5 (10%) patients.

Neutropenia developed in a 90-year-old man after 43 days of meropenem infusion, and resolved after cessation of the antibiotic. The 86-year-old woman who experienced nephrotoxicity had a history of chronic renal impairment and was taking voriconazole concomitantly; when switched to intermittent meropenem dosing her renal impairment resolved. There were no peripherally inserted central catheter (PICC) related adverse events, infusion reactions, neurotoxicity, or deaths ascribed to the meropenem therapy.

• Zobell et al describe the case report of a 13-year-old girl who was hospitalized with acute pulmonary exacerbation of her cystic fibrosis and was initially treated with intermittent meropenem 500 mg every 8 hr (51 mg/kg/day) along with once daily tobramycin. When she did not respond to this therapy, the total intermittent daily dose of meropenem was converted to continuous infusion, which was infused over 23.5 hours; the tobramycin was continued. Pulmonary function tests improved to baseline values, and there were no changes from baseline values of white blood count, platelet count, renal function or liver function tests.

• Feher et al performed a retrospective observational study in febrile neutropenic patients, comparing the clinical outcome after a 4 hour extended infusion of meropenem with that from the usual 30 minute infusion. Eighty-five patients received meropenem 1 g/8h over 30 minutes, and 76 received the same dose over 4 hours. Kaplan-Meier survival analysis showed a more prompt defervescence and a faster decrease in C-reactive protein in the extended infusion group, who also required half as many additional antibiotics as the shorter infusion group.

• A poster presented by Wright & Shepherd reported a retrospective cohort study in which 250 patients were given meropenem 1 gram every 8 hours and compared with 250 patients who were given an off-label dosing schedule of meropenem 500 mg every 6 hours. They found the ICU mortality to be 21.6% in the traditionally treated group, compared to 26.9% in the alternative dosing group. The authors concluded that such alternative dosing of meropenem in the critically ill appears to be associated with an increased rate of mortality.

e) Off-Label indication for meropenem

• Park et al conducted a retrospective cohort study of children with uncomplicated Gram-negative bacteremia, comparing clinical outcomes of receiving short (7-10 days) versus prolonged (>10 days) duration of various antibiotic agents (meropenem, piperacillin/tazobactam, ceftriaxone, cefepime, and aztreonam). Thirty of 170 patients received meropenem therapy (unknown dosing) for less than 10 days and 34 of 170 received meropenem for greater than 10 days.

There were 11 deaths amongst all the children, 6 and 5 in the short and long duration groups respectively, but it is not reported which antibiotics these children received. There were no specific adverse reactions associated with the specific antibiotic agents reported, but the authors concluded that the longer use may be associated with an increased risk of candidemia.

• Ning et al report findings for the treatment of nine adult patients with extensive burns complicated by pan-drug resistant *Acinetobacter baumannii*, an organism considered resistant to all currently available carbanems. The triple antibiotic therapy consisted of meropenem IV four times per day (6 g/day total) and cefoperazone-sulfactam twice a day (12 g/day total; cefoperazone 8 g and sulbactam 4 g) with the antibiotic infusion times prolonged to 1.5-2 hours every time; and minocycline, the first dose being 200 mg orally and then 50 mg every 6 hours thereafter. Comparison of lab results before and after treatment showed no elevation of serum creatinine, ALT or AST. The ALT and AST were elevated in five patients during the time of antibiotic therapy but this was felt due to other reasons, such as operation and infection. The treatment was effective in all nine patients even though the *Acinetobacter* was not susceptible to carbanem antibiotics in susceptibility testing.

• Meropenem is approved for empiric treatment of febrile neutropenia in Japan but Merrem® is not FDA-approved for this treatment. A prospective randomized study by Kobayashi et al was carried out to clarify the usefulness of meropenem with or without I.V. immunoglobulin as second line-therapy for pediatric febrile neutropenia.

Sixty-one patients, ranging in age from 0 to 22 years, with 146 febrile neutropenic episodes, were enrolled in this second-line study. Meropenem was given at 60 mg/kg per day (maximum dose: 1.5 g/day) as a 1 hour intravenous infusion three times per day in the August 2008- April 2010 period, and at 120 mg/kg per day (maximum dose: 3 g/day) as a 1 hour intravenous

infusion three times per day in the April 2010- April 2012 period. Adverse effects, described as liver dysfunction, were observed in six patients, four of whom had received only meropenem, and two of whom had received both meropenem and immunoglobulin. All six patients received meropenem at the 120 mg/kg dosing. Five of the six adverse events were classified as grade 2 and one patient was grade 3, using the Common Terminology Criteria for Adverse Events grading criteria.

- Sezgin et al performed a retrospective study comparing the efficacy of meropenem and piperacillin-tazobactam monotherapies in febrile neutropenic children with cancer. In 198 episodes, meropenem 60 mg/kg/day was given intravenously in three divided doses and results compared with 86 episodes treated with piperacillin-tazobactam 360 mg/kd/day administered in similar fashion. No adverse effects were observed due to either treatment and the two treatments were concluded to be equally effective and safe for the initial treatment of febrile neutropenia.

- Luyt et al conducted a prospective observational study in 169 patients who developed *Pseudomonas aeruginosa* ventilator-assisted pneumonia (VAP). Of these, 88 were treated with a carbanem: 24 with meropenem, 32 with imipenem, and 32 with doripenem. Among the 22 patients who had meropenem-susceptible strains, 5 died and 3 had VAP recurrence. Although carbapenem resistance emerged similarly among patients treated with any carbanem, in the case of recurrence, some imipenem-resistant strains remained meropenem and/or doripenem susceptible. No adverse effects of the therapies were reported.

f) Interaction with valproic acid

The Merrem® package insert states that "the concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended" because a resulting interaction may cause the valproic acid concentrations to drop below the therapeutic range, thereby increasing the risk of breakthrough seizures. A review by Rosche et al confirms this warning without reporting any new safety concerns.

A case report by Halacova et al confirms the need for this warning in the case of a 28-year-old woman who was given I.V. meropenem 1 gm four times daily for *Klebsiella* pneumonia, resulting in a lowered valproic acid level. No additional adverse effects were reported.

Unpublished Clinical Data

The Applicant conducted a search of Clinical Trials.gov, a U.S. National Institutes of Health registry and results database of publicly and privately supported clinical studies of human participants. This search found 66 studies for meropenem. Of these, only three had available data.

Of the three trials with available data, one had been terminated early per business decision. This study enrolled ten children hospitalized with complicated intraabdominal infections and treated

with meropenem. While no serious adverse events were described, one of the 10 children was reported with prolonged QT on electrocardiogram. It was not reported if the investigator felt this was related to meropenem.

A second trial enrolled two adults with complicated urinary tract infections who were treated with meropenem. This study had been terminated due to feasibility and low enrollment concerns. There were two serious events, shortness of breath and chest pain. It was not reported if the investigator felt either of these events was related to meropenem.The remaining completed study of young infants with intra-abdominal infections, which discusses off-label use of meropenem, was published in 2012 prior to the time period being reviewed.

Specific Safety Information of Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container:

The high sodium content of this product triggered the inclusion of this information under " WARNINGS AND PRECAUTIONS" section of the product label. (Note: Please see the full labeling text below.)

Clinical Comment: As previously mentioned in the clinical review (DARRTS, dated 06/23/2014) for the first cycle of this NDA submission, it is clinically important to add appropriate labeling revisions regarding sodium retention and patient monitoring in high-risk populations (i.e., patients with congestive heart failure).

4. Labeling Review

The clinical reviewer performed a review of the submitted a revised labeling for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container. The following revisions were accepted by the applicant on April 10, 2015. (Please note that other disciplines had other revisions to the label which are not mentioned in this review.)

1.In the FULL PRESCRIBING INFORMATION CONTENTS section:

- Relocation of the Drug-resistant bacteria text below this section and placing it under the newly added "1.4 Usage" heading.
-Addition of "5.11 High Sodium Load" heading.

2. Provide number to the tables ("Table 1 and Table 2") under DOSAGE AND ADMINISTRATION section.

3. In the "CONTRAINDICATIONS" section, the following text regarding sodium has been deleted. (b) (4)

(b) (4)

4. In the WARNINGS AND PRECAUTIONS" section, the text regarding administration of solutions containing sodium ions has been revised as follows:

"5.11 High Sodium Load

Each 500 mg of Meropenem for Injection USP and Sodium Chloride Injection USP delivers 245.1 mg (10.7 mEq) of sodium and each 1 gram of Meropenem for Injection USP and Sodium Chloride Injection USP delivers 290.2 mg (12.6 mEq) of sodium. Avoid use of Meropenem for Injection USP and Sodium Chloride USP in patients with congestive heart failure, elderly patients and patients requiring restricted sodium intake."

5. In the CLINICAL STUDIES" section, all tables were provided with titles and numbers.

6. In the "PATIENT COUNSELING INFORMATION" section, revised the beginning of the sentence into active voice. The adverse reaction "delirium" was added after the word "seizures" under the fourth bulleted paragraph. A fifth bulleted paragraph regarding the high sodium load information for patients was added:

"• Meropenem for Injection USP and Sodium Chloride Injection USP contains a high sodium load. Instruct patients to inform or report symptoms of difficulty breathing, swelling, or increased weight [see Warnings and Precautions (5.11)]."

7. Minor editorial revisions included: changed "g" abbreviation to word "gram" for clarity; and symbols of < and > were changed to words as " less than " and "greater than ", respectively; update the numbering of tables throughout the package insert; and update species of some bacteria; and update the Clinical and Laboratory Standards Institute (CLSI) references.

8. The background colors used on the container label of the 500 mg and the l g strength. were revised by the applicant per FDA recommendation to clearly differentiate the two strengths.

Clinical Comment: This amended Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container label will be revised accordingly upon receipt of the revised innovator drug (MERREM® I.V.) label to reconcile the two labels. Regarding the revised background colors on the container labels, the Division awaits the review and recommendations from the Division of Medication Error Prevention and Analysis and CMC.

5. Clinical Reviewer Conclusion and Recommendation

Based on review of the safety information, one CNS adverse reaction, delirium asociated with meropenem was identified in a patient who received meropenem for treatment of UTI and urosepsis (off-label use of meropenem). Although delirium is a labeled adverse reaction (6.1 Adverse Reactions from Clinical Trials subsection). this CNS adverse reaction should also be mentioned under Warnings and Precautions (5.10 Potential for Neuromotor Impairment subsection). Hypomagnesemia and increased GGT were identified as new adverse laboratory reactions in a clinical trial publication. The FDA will monitor these adverse reactions and no labeling changes are warranted at this time. A report from a recent publication notes that the incidence of liver and renal adverse reactions, and possibly convulsions appear higher than mentioned in the RLD package information, however, these reports were from patient populations that are different than the population enrolled in clinical studies. The FDA will continue to monitor these adverse reactions from the RLD core data reports but no labeling changes are warranted at this time.

From the clinical standpoint, this NDA is recommended for approval.

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/s/

ALMA C DAVIDSON
04/27/2015

HALA H SHAMSUDDIN
04/27/2015

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	202106
Applicant Name	B. Braun Medical Inc.
Date of Submission	September 27, 2013
PDUFA Goal Date	July 27, 2014
Established (USAN) Name	Meropenem for Injection USP and Sodium Chloride Injection USP in Duplex® Container
Dosage Forms / Strength	500 mg of Meropenem for Injection and 50 mL of Sodium Chloride 1 g of Meropenem for Injection and 50 mL of Sodium Chloride
Proposed Indications	Complicated skin and skin structure infections Complicated intra-abdominal Infections Bacterial meningitis
Recommended Action:	Complete Response

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Pharmacology Toxicology Review	Amy Ellis PhD
Chemistry Manufacturing and Controls Review	Lin Qi PhD
Biopharmaceutics Review	Elsbeth Chikhale PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Alma Davidson MD
Statistical Review	Margaret Gamalo PhD
Product Quality Review	Vinayak Pawar PhD
Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Ryan Owen PhD
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D
Labeling Review	Carrie Newcomer PharmD

1.0 Introduction

NDA 202106, Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container was submitted by B. Braun Medical Inc. This NDA was submitted as a 505(b)(2) application and the listed drug is Merrem® (meropenem hydrochloride) Injection, 500 mg/vial and 1 gram/vial (NDA 50706), held by Astra Zeneca Pharmaceuticals. Merrem is approved for the treatment of the following infections:

- Complicated skin and skin structure Infections
- Complicated intra-abdominal infections
- Bacterial Meningitis

2.0 Background

The proposed drug product, Meropenem for Injection USP and Sodium Chloride Injection USP, is a new formulation of meropenem hydrochloride intravenous solution supplied in a Duplex® Container. The drug product differs from the listed drug in the diluent that can be used for reconstitution. With this drug product, only the diluent (Sodium Chloride Injection, 0.9%) supplied in the proposed packaging system (Duplex® Container) can be used, whereas Merrem can be reconstituted with other commercially available compatible diluents as listed in the Merrem labeling. No clinical data have been submitted in this application. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed drug product. The applicant has requested a waiver for conducting in-vivo bioequivalence studies based on 21 CFR 320.22 (b).

The review team has completed their reviews of this application. For a detailed discussion of NDA 202106, please refer to discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Lin Qi, Ph.D., and the product quality microbiology reviewer is Vinayak Pawar, Ph.D.

Meropenem for Injection (Sterile Bulk) is a sterile mixture of meropenem trihydrate and sodium carbonate (b) (4) and is manufactured by (b) (4) For CMC information regarding Meropenem for Injection (Sterile Bulk) such as characterization, description of the manufacturing process, process controls, and stability, reference is made to DMF Type II (b) (4) held by (b) (4) with a Letter of Authorization (LoA). A recent review of DMF (b) (4) dated June 20, 2014 found it adequate to support the current NDA, pending an acceptable recommendation from the product quality microbiology reviewer.

The proposed drug product, Meropenem for Injection USP and Sodium Chloride Injection USP, is sterile, nonpyrogenic, and packaged in a single use, Duplex® Container. The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal. The applicant had proposed a filling overage of (b) (4)% which was not found to be acceptable and was subsequently revised by the applicant t (b) (4)%. This was found acceptable by Dr. Qi.

The Duplex® Container is designed to separate the sterile drug powder from the sterile diluent during manufacture. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber. This opens the peelable seal, releasing the diluent into the drug chamber, allowing Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system. The entire reconstitution process takes place in a closed, self-contained, sterile and needle free system.

Stability information submitted for the drug product includes six-month accelerated and twelve-month long-term data for three registration batches of the drug product (for both, 500 mg and 1 g strengths) manufactured at the proposed commercial manufacturing facility. The following expiration dating was found acceptable by Dr. Qi:

- Manufacture Configuration (intact): 24 months
- After removal of foil strip: 7 days
- After activation:
    - 1 hour at room temperature (25°C (b) (4))
    - 15 hours under refrigeration (5°C (b) (4))

In an amendment submitted to DMF (b) (4) the DMF holder had provided information about a newly constructed manufacturing plant (b) (4) The sterility assurance information pertaining to (b) (4) procedures and specifications for process simulation, container-closure and package integrity for (b) (4) was provided in DMF (b) (4) and found acceptable. From a product quality microbiology standpoint, Dr. Pawar found the application to be adequate and recommends approval.

The drug substance manufacturing facility (b) (4) was found acceptable by the Office of Compliance. However, Dr. Lin conveyed several concerns regarding the drug product manufacturing process to the FDA Investigator for evaluation during inspection of the drug product manufacturing facility located at the Facta Farmaceutici S.p.A., in Teramo, Italy. As a result of the recent inspection, this facility is currently under an OAI alert and the overall recommendation by the Office of Compliance on 07/17/2014 is withhold.

Dr. Qi recommended that the NDA not be approved based on the unacceptable status of the drug product manufacturing facility. In an addendum dated 07/24/14, Dr. Qi recommends that from a CMC perspective, the NDA not be approved.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Amy Ellis PhD. Dr. Ellis recommends approval of the NDA, provided that the CMC reviewer agrees with the applicant's assessment that the product does not contain any impurities or degradation products that need to be qualified by nonclinical testing. Dr. Ellis also found the labeling for Sections 8.1 and 13 adequate with a few editorial revisions.

5.0 Biopharmaceutics

Elsbeth Chikhale, PhD is the biopharmaceutics reviewer for this application. The applicant has requested a waiver of the requirement for submission of data from an in vivo bioequivalence study in accordance with 21 CFR 320.22(b). Dr. Chikhale agrees with the request and recommends approval of the NDA.

6.0 Clinical Microbiology

Kerian Grande Roche, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Dr. Grande Roche has provided labeling revisions that have been incorporated in the Division's proposed labeling.

7.0 Clinical Pharmacology

Ryan Owen, PhD, is the clinical pharmacology reviewer for this application. No new clinical pharmacology information was submitted in the NDA. Dr. Owen found the application to be acceptable from a clinical pharmacology standpoint and has provided edits to labeling that have been incorporated in the Division's proposed labeling.

8.0 Clinical Efficacy/Safety

Alma Davidson, MD, is the clinical reviewer for this application. No new clinical or statistical information was submitted in this NDA. The applicant submitted data from the literature to support their proposed revisions to the Contraindications and Warnings and Precautions sections of labeling regarding sodium chloride in the drug product. One gram of the proposed drug product will deliver a total sodium content of 290.2 mg (12.6 mEq), and 500 mg will deliver a total sodium content of 245.1 mg (10.7 mEq). When reconstituted with 5% dextrose, a 1 gram Merrem vial will deliver 90.2 mg (3.92 mEq) of sodium as sodium carbonate and the 500 mg vial will deliver 45.1 mg of sodium as sodium carbonate (1.96 mEq).The applicant is proposing

the addition of the following language to the Contraindications and Warnings and Precautions sections of the package insert to address the issue of a higher sodium content with the proposed drug product:

Contraindications Section

(b) (4)

Warnings and Precautions Section

(b) (4)

Dr. Davidson found these revisions acceptable and recommends approval of the NDA.

Margaret Gamalo, PhD, is the statistical reviewer for this application. No new clinical data were submitted with this application. Dr. Gamalo deferred a decision on this application to other review disciplines.

9.0 Labeling

Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) has provided a review of the proposed labeling. Dr. Winiarski's recommendations for labeling have been communicated to the applicant and incorporated in labeling. Carrie Newcomer, PharmD, from the Office of Prescription Drug Promotion (OPDP) has provided labeling recommendations that have been incorporated in the labeling proposed by the Division.

10.0 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.

11.0 Other Regulatory Issues

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC) as there were no issues requiring input from the AIDAC. There are no other relevant regulatory issues for this application.

12.0 Recommended Regulatory Action

I agree with the recommendations made by Dr. Qi that a complete response action should be taken as the drug product manufacturing facility is listed as OAI and the overall recommendation from the Office of Compliance is withhold.

The deficiency to be communicated to the applicant is as follows:

During a recent inspection of Facta Farmaceutici S.p.A., in Teramo, Italy, the drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
07/25/2014

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	September 25, 2013
PDUFA Goal Date	July 27, 2013
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:	*Complete Response*

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 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".

2. Background

Meropenem is a synthetic, carbapenem antibacterial 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. CMC/Device

The CMC Reviewer was Lin Qi, Ph.D., and the Product Quality Microbiology Reviewer was Vinayak B. Pawar, Ph.D. Their findings are summarized below.

Meropenem for Injection (Sterile Bulk) is manufactured by [redacted] (b) (4) It is a sterile mixture of Sterile Meropenem Trihydrate and Sodium Carbonate [redacted] (b) (4)

For CMC information for Meropenem for Injection (Sterile Bulk) such as a characterization, description of the manufacturing process, process controls, stability, etc., a reference is made to DMF Type II (b) (4) for Meropenem for Injection (Sterile Bulk) held by (b) (4) with a Letter of Authorization (LoA) located in NDA Module 1.4.1. The most recent review of DMF (b) (4) dated June 20, 2014 in DARRTS found it adequate to support the current NDA.

The proposed drug product, Meropenem for Injection USP and Sodium Chloride Injection USP, is sterile, nonpyrogenic and packaged in a single use, dual chamber container, i.e., Duplex® Container. The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber. This opens the peelable seal, releasing the diluent into the drug chamber. This allows the active pharmaceutical ingredient, Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system.

The manufacturing process consists of several stages, which include: (b) (4) Three registration batches of 500 mg and 1 g product strength were manufactured and placed on stability. The proposed commercial batch size is based upon a (b) (4) increase of the registration batches (i.e., (b) (4) units).

The drug product (Meropenem for Injection, USP) specification includes tests for appearance, identification, constituted solution, particulate matter, clarity of solution, color of solution, pH, reconstitution time, loss on drying, assay, uniformity of dosage, impurities, content of sodium, filling weight, filling volume, sterility, and bacterial endotoxin. The diluent (Sodium Chloride Injection, USP) is controlled by testing appearance, identification, assay, iron, pH, and heavy metals, with the sterility and bacterial endotoxin tests performed on the reconstituted solution. No residual solvents or metal catalysts are introduced during the manufacturing of the drug product, since the drug product contains only the drug substance.

As mentioned above, the drug product manufacturing process includes (b) (4) These aspects of the manufacturing process, as well as integrity of the container closure system, and the proposed microbiological quality attributes in the drug substance and the drug product specifications were evaluated by the Product Quality Microbiology Reviewer, Dr. Vinayak B. Pawar who recommended this NDA for approval from the product quality microbiology standpoint (review dated June 30, 2014 in DARRTS).

Stability information submitted for the drug product includes six-month accelerated and twelve-month long term data for three registration batches of the drug product (for both, 500 mg and 1 g strengths) manufactured at the proposed commercial manufacturing facility. Based on these data, an expiration dating period of 24 months was assigned for the unactivated drug product in the proposed commercial container closure system when stored at controlled room temperature 20–25°C (68–77°F). In addition, the labeling includes a recommendation that after

reconstitution, the product should be used within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

The drug substance manufacturing facility (b) (4) was found acceptable by the Office of Compliance. However, Dr. Lin conveyed several concerns regarding the drug product manufacturing process to the FDA Investigator for evaluation during inspection of the drug product manufacturing facility located at the Facta Farmaceutici S.p.A., in Teramo, Italy. As a result of the recent inspection, this facility is currently under an OAI alert and the overall EES site recommendation for this NDA is pending.

Dr. Qi recommended a non-approval based on the pending product quality microbiology review and unacceptable status of the drug product manufacturing facility. For details of this conclusion, refer to her review dated June 20, 2014 in DARRTS. It should be noted that the product quality microbiology review is now in DARRTS (recommending Approval, as stated above). However, an Overall Recommendation from the Office of Compliance for this NDA is still pending at this time.

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Ellis Ph.D.was the Pharmacology/Toxicology Reviewer for this application and concluded that from the nonclinical pharmacology standpoint, the NDA can be approved (for details refer to the review dated May 22, 2014 in DARRTS).

The applicant did not conduct any nonclinical studies in support of this NDA. Dr. Ellis stated that unless the impurity profile of this formulation of meropenem differs significantly from the previous formulation, there are no pharmacology/toxicology issues with this drug. In addition, the labeling does not differ from the listed drug and there are only a few editorial changes recommended from the pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Elsbeth Chikhale, Ph.D., was the Biopharmaceutics Reviewer and Ryan Owen, Ph.D., was the Clinical Pharmacology Reviewer for this application. Their findings and recommendations are summarized below.

This NDA includes a bioequivalence (BE) waiver request for the proposed drug product. The focus of the biopharmaceutics review is on the evaluation and acceptability of the data supporting the approval of the BE waiver request. Dr. Chikhale noted in her review that although the volumes of the diluents for the listed drug and the proposed drug product are different, the concentration of the active (and inactive) ingredients in the final solution for intravenous administration will be in the same range of 1 to 20 mg/mL for the proposed drug product and the listed drug product. In addition, the difference in the container closure system is not expected to change the bioavailability or bioequivalence. Therefore, Dr. Chikhale concluded that the in vivo BA/BE of the proposed Meropenem for Injection USP and Sodium

Chloride Injection USP in the Duplex Container is considered self-evident, and the Applicant's request for a waiver of the submission of in vivo BE data for their proposed drug product is acceptable. Therefore, the biowaiver is granted and this NDA is recommended for approval from the biopharmaceutics perspective (review dated June 2, 2014 in DARRTS).

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. Dr. Owen's review includes several recommendations to the clinical pharmacology section of the labeling (for details refer to review dated June 20, 2014 in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application and the Microbiology Reviewer recommends approval of this application from the microbiology standpoint. However, several edits in the product package insert have been recommended which include an update to the references and the removal of the organisms from the lists that are associated with bacterial meningitis, since bacterial meningitis is no longer indicated for meropenem (refer to the review dated May 14, 2014 in DARRTS).

7. Clinical/Statistical - Efficacy

Alma Davidson, MD, was the Clinical Reviewer, and Margaret Gamalo, Ph.D., was the Statistical Reviewer for this NDA.

This 505(b)(2) NDA does not contain any clinical studies as the Applicant is relying on the FDA prior determination of efficacy and safety of the listed drug (Merrem® IV) for the listed indications.

In her recommendation, Dr. Davidson stated that risk/benefit assessment for this drug product has been demonstrated and supported by prior evidence and experience with Merrem® IV. In addition, based on a literature review on the safety of saline solutions, there is no substantial additional risk associated with this formulation when used as prescribed for the proposed adult indications. Therefore, Dr. Davidson recommends this application for approval with several recommended revisions to the proposed labeling (for details refer to the review dated June 23, 2014 in DARRTS).

Dr. Gamalo indicated that no statistical review was needed for this application as there were no clinical studies submitted in this NDA (review dated May 12, 2014 in DARRTS).

8. Safety

As stated above, the Applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug. In addition, as requested by the Agency, the Applicant provided the literature review in support of the labeling changes proposed under the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections regarding statements of solutions containing sodium ions. Information provided by the Applicant includes ten published articles and the sodium chloride injection labeling.

Based on the review of this information, the Applicant concluded that (b) (4) Dr. Davidson agreed with the Applicant's assessment and the proposed labeling revisions regarding sodium retention and patient monitoring in high-risk populations (i.e., patients with congestive heart failure). Dr. Davidson also stated that (b) (4) such labeling is not warranted for this product.

For details regarding safety assessment of the proposed drug product and recommended labeling revisions, refer to the review by Dr. Davidson (dated June 23, 2014 in DARRTS).

9. Advisory Committee Meeting

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

10. 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.

11. 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.

12. Labeling

The Applicant provided a proposed product label based on that of the LD, Merrem® IV, with information in PLR format.

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors and provided several recommendations to the labeling and the container label (review in DARRTS dated June 10, 2014). They include the following recommendations for the Applicant regarding the container label: 1) replacing the (b) (4) abbreviation with the word "Intravenous"; 2) ensuring that the established name and strength are the most prominent information on the PDP by increasing their font size and that the units of measure are next to the numbers (e.g. 500 mg) in the strength statement for clarity; 3) increasing the prominence of important statements like "For Intravenous Infusion Only, "Use only after mixing contents of both chambers", and "Single dose" by increasing their font size and placing each statement on a separate line; 4) including the lot number and expiration date; 5) deleting the reference number (REF 3183-11); 6) decreasing the font size of the NDC number and relocating it such as to the upper right corner of the label; and 7) revising the order of several sections to list the "Prior to Reconstitution" section first, followed by "Reconstitution" section and "After Reconstitution" section. In addition, DMEPA also recommended replacing symbols such as '>', '≥', '<' with applicable words, such as "greater than" or "less than", etc. and the hyphen between numbers (e.g. 26-50) with the word "to" in the following sections of the labeling: Dosage and Administration Sections, Highlights of Prescribing Information and Full Prescribing Information.

In addition, several comments and recommendations were obtained from the Office of Prescription Drug Promotion (OPDP) (review dated July 2, 2014 in DARRTS).

It should be noted that a review and discussions with the Applicant regarding the labeling and the container label are pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  I concur with the assessments made by the review team and recommend the issuance of a Complete Response for this NDA.

- Risk Benefit Assessment

  The risk-benefit assessment for this application focused on the significant manufacturing issues identified during the review cycle, specifically, significant CGMP issues revealed during a recent inspection of the drug product manufacturing facility.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Not applicable

- Recommendation for other Postmarketing Study Commitments

  Not applicable

- Recommended Comments to Applicant

  The following deficiency should be included in the Complete Response letter:

  During a recent inspection of the Facta Farmaceutici S.p.A. (Teramo, Italy) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. (DRAFT)

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/s/

DOROTA M MATECKA
07/05/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202106
Priority or Standard	S
Submit Date(s)	September 27, 2013
Received Date(s)	September 27, 2013
PDUFA Goal Date	July 27, 2014
Division / Office	DAIP/OAP
Reviewer Name(s)	Alma C. Davidson, M.D.
Review Completion Date	June 20, 2014
Established Name	Meropenem
(Proposed) Trade Name	Meropenem for Injection, USP and Sodium Chloride Injection USP in the Duplex Container
Therapeutic Class	Carbapenem
Applicant	B. Braun Medical Inc.
Formulation(s)	Solution for Injection
Proposed Dosing Strength	500 mg and 1 gram
Indication(s)	Complicated Skin and Skin Structure Infections Complicated Intra-abdominal Infections Bacterial Meningitis
Intended Population(s)	Adults and Pediatric patients (≥3 months) requiring full adult dose only

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

The Applicant, BBraun Medical Inc., has submitted this 505(b)(2) new drug application (NDA) for Meropenem for Injection, USP and Sodium Chloride Injection,USP in the Duplex Container using the AstraZeneca product, NDA 50706 MERREM®I.V., as the reference listed drug (RLD).There are no clinical trials conducted by the Applicant to support this 505(b)(2) NDA for Meropenem for Injection, USP and Sodium Chloride Injection, USP in Duplex Container. The review for this NDA relies on the prior FDA determination of effectiveness and safety of meropenem based on studies which were not conducted by or for the Applicant.

1.1 Recommendation on Regulatory Action

From the clinical standpoint, this application is recommended for approval. The Meropenem for Injection, USP and Sodium Chloride Injection, USP in the Duplex Container label in Physician's Labeling Rule (PLR) format is under review by the different disciplines.

1.2 Risk Benefit Assessment

Risk/benefit assessment for this drug product has been demonstrated and supported by prior evidence and experience with the RLD (MERREM®I.V.). Based on a literature review on the safety of saline solutions, there is no substantial additional risk associated with this formulation when used as prescribed for the proposed adult indications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division does not recommend any postmarket risk evaluation and mitigation strategies at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division does not recommend any postmarket requirement and commitment at this time.

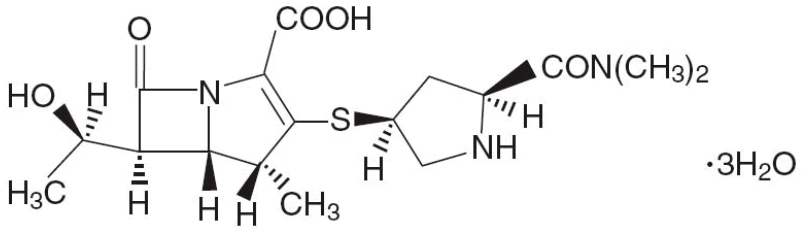
2 Introduction and Regulatory Background

Meropenem is a synthetic, broad-spectrum, carbapenem antibacterial for intravenous administration.

2.1 Product Information

Meropenem for injection is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibacterial for intravenous administration. Its chemical name is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. I

Structural formula:



Empirical formula: $C_{17}H_{25}N_3O_5S \cdot 3H_2O$

Molecular weight: 437.52.

RLD (USA) Approved Dosage Strength: MERREM® I.V. (meropenem for Injection), 500 mg/vial and 1g/vial.

Applicant's Proposed Dosage Strength: Meropenem for Injection, USP and Sodium Chloride Injection,USP in the Duplex Container, 500 mg and 1 gram strengths.

Applicant's proposed indications, dosing regimens, age groups: The Applicant's product, Meropenem for Injection, USP and Sodium Chloride Injection,USP in the Duplex Container, has the same proposed two indications (Complicated skin and skin structure infections and Complicated intra-abdominal infections), adult dosing regimens, except for pediatric dosing and bacterial meningitis indication as the RLD, MERREM®I.V.

2.2 Tables of Currently Available Treatments for Proposed Indications

No new proposed indications are included in this application.

2.3 Availability of Proposed Active Ingredient in the United States

Meropenem is a synthetic, broad-spectrum, carbapenem antibacterial for intravenous administration commercially available in the USA as 500 mg /vial and 1 gram /vial strengths.

2.4 Important Safety Issues With Consideration to Related Drugs

Meropenem is the synthetic, broad-spectrum, carbapenem antibacterial approved by FDA in 1996 for intravenous administration. There are recent efficacy and safety labeling changes to the RLD, MERREM® I.V. (meropenem for Injection) label as of December 16, 2013 which include:

- In the **DOSAGE AND ADMINISTRATION** section:
  - **2.1 Adult Patients**
  - The recommended dose of MERREM I.V. is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. When treating complicated skin and skin structure infections caused by *P.aeruginosa*, a dose of 1g every 8 hours is recommended.
  - **2.3 Use in Pediatric Patients (≥ 3 Months only)**

    When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 g for pediatric patients weighing over 50 kg) every 8 hours is recommended.
  - **2.6 Stability and Storage**

    Freshly prepared solutions of MERREM I.V. should be used. However, constituted solutions of MERREM I.V. maintain satisfactory potency under the conditions described below. Solutions of intravenous MERREM I.V. should not be frozen.

    Intravenous Bolus Administration

    MERREM I.V. injection vials constituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of MERREM I.V.) may be stored for up to 3 hours at up to 25°C (77°F) or for 13 hours at up to 5°C (41°F).

Solutions prepared for infusion (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25°C (77°F) or 15 hours at up to 5°C (41°F).

Solutions prepared for infusion (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) constituted with Dextrose Injection 5% should be used immediately.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following regulatory activities are related to this submission:

(MO Comment: The review Division in 2010 was the Division of Anti-infective and Ophthalmology Products (DAIOP). After the reorganization, the DAIOP became the Division of Anti-Infective Products (DAIP).

- On August 9, 2010 the Sponsor (B.Braun) requested a Type B meeting with the Division of Anti-Infective and Ophthalmic Products (DAIOP) to discuss the design and implementation of the proposed contract manufacturing plan for this new Duplex product for which B. Braun intends to submit a 505(b)(2) application. According to the applicant, they will have a contract manufacturer, FACTA Farmaceutici S.p.A. located in Italy, to manufacture this product. FACTA was inspected by the FDA in October of 2009 and received an acceptable rating for vial manufacturing.

- On August 20, 2010, the DAIOP sent a letter to the Sponsor granting a Type B meeting to be scheduled for November 4, 2010 based on the Sponsor's statement of purpose, objectives, and proposed agenda.

- On September 30, 2010,the Sponsor sent a meeting package to the DAIOP.

- On October 26, 2010, the DAIOP sent preliminary responses to the Sponsor's questions for the meeting through an electronic mail communication.

- On November 4, 2010, a Face-to Face meeting between the FDA and the Sponsor was held and discussed the proposed NDA submission for Meropenem for Injection, USP and Sodium Chloride Injection, USP in Duplex Container as 505(b)(2) application.

- On December 16, 2010, the Sponsor's meeting minutes was sent to the DAIOP. The Sponsor accepted the FDA's meeting minutes with one

correction by the Sponsor, as to one of the Sponsor's attendees, (b) (6) who did not attend the meeting because she is no longer with the company.

- On September 25, 2013, the Applicant has submitted to the DAIP, this NDA 202106 for Meropenem for Injection, USP and Sodium Chloride Injection, USP in Duplex Container as a 505(b)(2) application.

- On June 19, 2014, the Applicant submitted a labeling amendment to this NDA 202106 Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container to match the RLD per a teleconference with the Division on June 11, 2014. This revised labeling includes the bacterial meningitis indication for pediatric patients ≥3 months of age requiring full adult dose only

.

2.6 Other Relevant Background Information

According to the Applicant, the formulation of Meropenem for Injection is based on the reference list drug (RLD), MERREM®. MERREM® is available as a 500 mg/vial injection and 1 gram/vial injection presentations in the US.

Pediatric Assessment:

The Applicant requested a full waiver of the requirement to submit pediatric assessments in connection with this NDA. The Applicant proposes to waive pediatric assessment requirements for all pediatric age groups that cannot receive the full dose. The full dose can only be delivered to pediatric patients that fit the criteria for the adult dose otherwise there is a potential safety issue (overdose) that exists which could render the product unsafe in that pediatric population. 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.

Additionally, the Applicant proposes to waive the pediatric assessment since this product fails to represent a meaningful therapeutic benefit over existing therapies (ex. vials) and is unlikely to be used in a substantial number of pediatric patients that cannot receive a full fixed dose. The Duplex® container is designed and limited to deliver the full dose and is not intended for partial delivery.

The Pediatric Research Equity Act (PREA) requirements do not apply as the proposed drug product 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Not applicable.

3.2 Compliance with Good Clinical Practices

Not applicable.

3.3 Financial Disclosures

No new clinical studies were conducted for this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final chemistry, manufacturing, and controls (CMC) review recommendation for this NDA is pending. (Note: The reader is referred to the CMC review by the chemistry reviewer, Dr. Lin Qi. for detailed descriptions of the drug product and manufacturing process.)

4.2 Clinical Microbiology

Note: The reader is referred to the microbiology review by the microbiologist, Dr. Kerian Grande for details.

4.3 Preclinical Pharmacology/Toxicology

There are no additional non-clinical toxicology studies conducted to support this application. Note: The reader is referred to the Pharmacology/toxicology review by Dr. Amy Ellis.

4.4 Clinical Pharmacology

The reader is referred to the clinical pharmacology review of Dr. Ryan Owen.

4.4.1 Mechanism of Action:

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*.

4.4.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this application.

4.4.3 Pharmacokinetics

There are no new pharmacokinetic data submitted with this application.

4.5 Statistical

There is no statistical issue with this application. Please see the brief statistical review by Dr. Margaret Gamalo-Siebers.

5 Sources of Clinical Data

No new clinical trials for an indication to support this 505(b)(2) new drug application for Meropenem for Injection, USP and Sodium Chloride Injection ,USP in Duplex Container for injection.

5.1 Tables of Studies/Clinical Trials

Not applicable.

5.2 Review Strategy

Not applicable.

6 Review of Efficacy

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Meropenem for Injection, USP and Sodium Chloride Injection ,USP in Duplex Container. The review for this NDA relies on prior FDA determination of effectiveness based on studies which were not conducted by or for the Applicant, B. Braun Inc. for the reference listed drug, MERREM®.

Efficacy Summary

Not applicable.

6.1 Indication

Not applicable.

6.1.1 Methods

Not applicable.

6.1.2 Demographics

Not applicable.

6.1.3 Subject Disposition

Not applicable.

6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

The Agency requested the Applicant to provide the literature review in support of the labeling changes proposed under the **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS** sections regarding statements of solutions containing sodium ions. According to the applicant, the rationale for the change in Contraindications/Warnings and Precautions sections statements for sodium chloride is based upon a literature review.

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Not applicable.

7.1.2 Categorization of Adverse Events

Not applicable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

Not applicable.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Not applicable.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

Not applicable.

7.3.1 Deaths

Not applicable.

7.3.2 Nonfatal Serious Adverse Events

Not applicable.

7.3.3 Dropouts and/or Discontinuations

Not applicable.

7.3.4 Significant Adverse Events

Not applicable.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

Not applicable.

7.4.1 Common Adverse Events

Not applicable.

7.4.2 Laboratory Findings

Not applicable.

7.4.3 Vital Signs

Not applicable.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

Not applicable.

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant requested a full waiver of the requirement to submit pediatric assessments in connection with this NDA. The Applicant proposes to waive pediatric assessment requirements for all pediatric age groups that cannot receive the full dose. The full dose can only be delivered to pediatric patients that fit the criteria for the adult dose otherwise there is a potential safety issue (overdose) that exists which could render the product unsafe in that pediatric population. 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.

Additionally, the Applicant proposes to waive the pediatric assessment since this product fails to represent a meaningful therapeutic benefit over existing therapies (ex. vials) and is unlikely to be used in a substantial number of pediatric patients that cannot receive a full fixed dose. The Duplex® container is designed and limited to deliver the full dose and is not intended for partial delivery.
.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions/Safety Issues

The Agency requested the Applicant to provide the literature review in support of the labeling changes proposed under the **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS** sections regarding statements of solutions containing sodium ions. According to the Applicant, the rationale for the change in contraindication/warning statements for sodium chloride is based upon a literature review and review of BBraun's Sodium Chloride Injections, USP label.

The Applicant provided the following articles and the sodium chloride injection label in support of the labeling changes are discussed below.

1. Burdett E, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev. 2012 Dec 12;12:CD004089.

This is a Cochrane review of the safety and efficacy of perioperative administration of buffered versus non-buffered fluids for plasma volume expansion or maintenance in adult patients undergoing surgery. The authors only included randomized trials of buffered versus non-buffered intravenous fluids for perioperative fluid resuscitation. The trials with other forms of comparisons such as crystalloids versus colloids and colloids versus different colloids, hypertonic fluids and dextrose-based fluids were excluded.

The authors analysis suggests that intravenous fluids containing a physiological buffer are a safe alternative to saline-based fluids in adult patients undergoing surgery. The pooled data from three studies suggest that the overall mortality was low and there was no evidence that the choice of fluids, either buffered or non-buffered, influenced mortality. For the secondary outcomes, there were no differences in renal dysfunction and surrogate markers of renal dysfunction (urine output and serum creatinine) between groups. Some of the other secondary outcomes did reveal statistically significant differences, including a reduced postoperative pH (pH 7.33 versus 7.39, $P < 0.00001$), an increased postoperative base deficit (base deficit of 5.0 versus 1.5, $P < 0.00001$), a reduced postoperative serum bicarbonate (serum bicarbonate of 19 mmol/L versus 22 mmol/L, $P < 0.00001$) and reduced PaC02 (PaC02 of 36.17 mmHg versus 37.35 mmHg, $P < 00001$) in the non-buffered group compared.

The non-buffered fluid group also had significantly greater base deficit, serum sodium and chloride levels. There was no difference demonstrated in length of hospital stay and no data were reported on cost or quality of life.

The authors concluded that administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids. The use of buffered fluids is associated with less metabolic derangement, in particular hyperchloremia and metabolic acidosis. However, larger studies are needed to assess robust outcomes such as mortality.

2. Vincent JL, Gottin L. Type of fluid in severe sepsis and septic shock. Minerva Anestesiol. 2011 Dec;77(12):1190-6.

This article reviews the advantages and limitations of the key fluid types currently used for the resuscitation of critically ill patients with sepsis, including cystalloids (saline solutions and Ringer's lactate), and the colloids (albumin, gelatins, dextrans, and hydroxyethyl starches) . The authors note: COPYRIGHT MATERIAL WITHHELD. Hypertonic saline solutions can induce fluid shifts from the intracellular to the extracellular compartment. They have been proposed for use as an early resuscitation fluid in patients with sepsis and may have valuable effects on restoration of intravascular volume, improvement of cardiac output, and improvement of regional microcirculation. Experimental studies have also suggested additional anti-inflammatory effects. However, further clinical studies are needed to confirm whether or not these fluids have a place in the resuscitation of patients with sepsis.

3. Prowle JR, Bellomo R. Fluid administration and the kidney. Curr Opin Crit Care. 2013 Aug;19(4):308-14.

This article focuses on recent studies examining fluid administration and renal function in critical illness to critically examine conventional justification for fluid administration. The authors note that: COPYRIGHT MATERIAL WITHHELD.

COPYRIGHT MATERIAL WITHHELD.

4. Muller L, Lefrant J-Y. Metabolic effects of plasma expanders .Transfusion Alternatives in Transfusion Medicine. 2010;11 (Suppl. 3), 10–21

The authors note COPYRIGHT MATERIAL WITHHELD.

5. Jivan D. Management of diabetic ketoacidosis. JEMDSA 2011;16(1):10-14

This article discusses the role of intravenous 0.9% saline in the management of diabetic ketoacidosis, noting that while use of saline is recommended in current treatment guidelines, use of large volumes could lead to hyperchloremic metabolic acidosis of uncertain clinical significance. He concludes COPYRIGHT MATERIAL WITHHELD.

6. Wujtewicz M. Fluid use in adult intensive care. Anaesthesiol Intensive Ther. 2012 Aug 8;44(2):92-5.

The author discussed the use of intravenous fluids in critical care medicine and commented: COPYRIGHT MATERIAL WITHHELD.

7. Srinivasa S, Hill AG. Perioperative fluid administration: historical highlights and implications for practice. Ann Surg. 2012 Dec;256(6):1113-8.

The authors in a historical use of the evolution of intravenous fluid therapy note: COPYRIGHT MATERIAL WITHHELD.

8. Redhi L. Fluids: what's new? S Afr Fam Pract 2013;55(3)(Suppl 1):S28-S31

The author notes that COPYRIGHT MATERIAL WITHHELD.

9. Day A, Rockall T. Fluid management. Surgery 2010; 28(4):151-4

The authors, reviewing fluid management in surgical patients comment that COPYRIGHT MATERIAL WITHHELD.

10. Leach R. Fluid management on hospital medical wards. Clin Med. 2010 Dec;10(6):611-5.

The author reports that inpatient fluid management again draws attention to the risk of hyperchloraemic metabolic acidosis if 0.9% saline is administered intravenously.

The Applicant concludes that (b) (4)

MO Comment: The reviewer concurs with the Applicant's assessment that it is clinically important to add appropriate labeling revisions regarding sodium retention and patient monitoring in high-risk populations (i.e., patients with congestive heart failure). The Applicant made the revisions to the Meropenem for Injection, USP and Sodium Chloride Injection, USP in Duplex Container (b) (4) ***such labeling is not warranted for this product.***

8 Postmarket Experience

The adverse events reported during the postmarket experience for meropenem are taken from the RLD, MERREM label:

“Hematologic - agranulocytosis, neutropenia, and leukopenia; a positive direct or indirect Coombs test, and hemolytic anemia.

Skin-toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiforme.”

9 Appendices

9.1 Literature Review/References

The following ten literature articles are provided by the Applicant:

In addition, the clinical reviewer looked at the B. Braun -Sodium Chloride Injection USP prescribing information and the RLD, MERREM® I.V., label.

1. Burdett E, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev. 2012 Dec 12;12:CD004089.

2. Vincent JL, Gottin L. Type of fluid in severe sepsis and septic shock. Minerva Anestesiol. 2011 Dec;77(12):1190-6.

3. Prowle JR, Bellomo R. Fluid administration and the kidney. Curr Opin Crit Care. 2013 Aug;19(4):308-14.

4. Muller L, Lefrant J-Y. Metabolic effects of plasma expanders .Transfusion Alternatives in Transfusion Medicine. 2010;11 (Suppl. 3), 10–21

5. Jivan D. Management of diabetic ketoacidosis. JEMDSA 2011;16(1):10-14

6. Wujtewicz M. Fluid use in adult intensive care. Anaesthesiol Intensive Ther. 2012 Aug 8;44(2):92-5.

7. Srinivasa S, Hill AG. Perioperative fluid administration: historical highlights and implications for practice. Ann Surg. 2012 Dec;256(6):1113-8.

8. Redhi L. Fluids: what's new? S Afr Fam Pract 2013;55(3)(Suppl 1):S28-S31

9. Day A, Rockall T. Fluid management. Surgery 2010; 28(4):151-4

10. Leach R. Fluid management on hospital medical wards. Clin Med. 2010 Dec;10(6):611-5

11. B. Braun Medical Inc.-Sodium Chloride Injection USP prescribing information

9.2 Labeling Recommendations

The Applicant made the following changes to the Meropenem for Injection, USP and Sodium Chloride Injection ,USP in Duplex Container in PLR format:

(MO Comment: The Applicant's proposed labeling revisions are highlighted in yellow in the attached label below.)

- Replacement of RLD, MERREM by ASTRAzENECA specific information with B.Braun Medical Inc. product name, Meropenem for Injection, USP and Sodium Chloride Injection ,USP in Duplex Container and IV route of administration.

- Addition of text under CONTRAINDICATIONS section, regarding the (b) (4)

- Addition of text under WARNINGS AND PRECAUTIONS section, regarding the administration of solutions containing sodium ions.

- Addition of text under the DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING sections, regarding description of the DUPLEX® container.

- In the Pediatric Use subsection and under DOSAGE AND ADMINISTRATION section, information regarding Meropenem for Injection, USP and Sodium Chloride Injection ,USP in Duplex Container which is designed to deliver in pediatric patients who require the full adult dose to prevent unintentional overdose is stated under this section.

- The Applicant removed the text for RLD's drug delivery form of bolus injection not applicable to B. Braun drug delivery form.

- Changed titles and subtitles as required for PLR format per Guidance for Industry, Labeling for Human Prescription Drug and Biological Products.

The clinical reviewer proposes the following changes to be added to the Meropenem for Injection, USP and Sodium Chloride Injection, USP in Duplex container label for consistency with the recent efficacy and safety labeling changes to the RLD, MERREM® I.V.(meropenem for Injection) label as of December 16, 2013:
(Note: Additions are underlined.)

- - In the HIGHLIGHTS OF PRESCRIBING INFORMATION section:

  - Under the development of drug-resistant bacteria paragraph, the word (b) (4) should be deleted because (b) (4)

  - Under "RECENT MAJOR CHANGES" subsection:

--------RECENT MAJOR CHANGES -----
-Dosage and Administration, Adult Patients (2.1)
-Dosage and Administration Use in Pediatric Patients (≥ 3 Months only)(2.3)

2.3 Use in Pediatric Patients (≥ 3 Months only)

When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 g for pediatric patients weighing over 50 kg) every 8 hours is recommended.

- The text referring to (b) (4) is deleted (b) (4)

- In the Geriatric Use subsection, the following language should be added regarding the clinical implication of sodium administration in the elderly population:

"Meropenem for injection in the DUPLEX® Container System contains 290.2 mg (12.6 mEq) of sodium per gram of Meropenem. At the usual recommended doses, patients would receive between 735 mg/day and 870 mg/day (32 mEq and 38 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.11)]."

30 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

(b) (4)

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALMA C DAVIDSON
06/23/2014

BENJAMIN D LORENZ
06/23/2014
Acting Team Leader

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202106 **Applicant:** B.Braun Medical Inc. **Stamp Date:** Sept. 27, 2013

Drug Name: Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container, 0.5 and 1g **NDA/BLA Type:** 505 (b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The applicant stated that the rationale for changes in the Contraindications and Warnings and Precautions sections regarding NaCl is based upon a literature review.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	The applicant submitted in Module 2 only for 2.3 Quality Overall Summary.
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?				
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				This application is a 505(b)(2).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			In Module 1: Section 1.9.1. The applicant provided a Request for Waiver of Pediatric Studies.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	There are no clinical studies conducted by the applicant.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes__X__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please provide the literature review in support of the labeling changes of your product under the Contraindications, Warnings and Precautions sections regarding statements of solutions containing sodium ions.

Alma C. Davidson, M.D. November 26, 2013
Reviewing Medical Officer Filing Date

Benjamin Lorenz, M. D. November 26, 2013
Acting- Medical Team Leader Filing Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALMA C DAVIDSON
11/20/2013

BENJAMIN D LORENZ
11/20/2013
Acting Team Leader