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RESEARCH**

APPLICATION NUMBER:

202106Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 202-106	Submission Date(s): 10/30/14
Drug	Meropenem
Trade Name	Meropenem for Injection, USP
OCP Reviewers	Ryan P. Owen, Ph.D.
OCP Team Leader	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	B. Braun
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	500 mg Meropenem for Injection USP and 50 mL Sodium Chloride Injection 0.9% USP in DUPLEX Container 1 g Meropenem for Injection USP and 50 mL Sodium Chloride Injection 0.9% USP in DUPLEX Container
Indication	cSSSI, cIAI, meningitis
Dosage and Administration	cSSSI (500 mg every 8 hours), cIAI (1 g every 8 hours), meningitis (2 g every 8 hours) Adults with Renal Impairment: Mild: No Change Moderate: Recommend dose given every 12 hours Severe: Half of the recommended dose given every 24 hours < 10 mL/min: Half of the recommended dose given every 24 hours Pediatric dose: Pediatric patients weighing over 50 kg should receive the adult dose. There is no recommended dosing for pediatric patients weighing less than 50 kg for this product.

1. EXECUTIVE SUMMARY

B. Braun submitted a 505(b)(2) New Drug Application (NDA) on 9/27/13 for Meropenem for Injection and Sodium Chloride for Injection in a duplex container (NDA 202-106). Meropenem is FDA approved for the treatment of complicated skin and skin structure infections at a dose of 500 mg q8h and for complicated intra-abdominal infections at a dose of 1 g q8h. The Sponsor (B. Braun) is seeking approval for 500 mg and 1000 mg meropenem duplex containers. NDA 202-106 received a complete response letter on 7/25/14 citing facility inspections. The Sponsor resubmitted their NDA on 10/30/14 claiming that the facility issues have been resolved. From a clinical pharmacology standpoint, the only new information is a revised label. The proposed labeling changes in the sections relevant for clinical pharmacology are acceptable.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology components of this NDA and is recommending that this application be approved.

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/s/

RYAN P OWEN
03/13/2015

KIMBERLY L BERGMAN
03/13/2015

CLINICAL PHARMACOLOGY REVIEW

NDA: 202-106	Submission Date(s): 9/27/2013
Drug	Meropenem
Trade Name	Meropenem for Injection USP and Sodium Chloride for Injection USP
OCP Reviewers	Ryan P. Owen, Ph.D.
OCP Team Leader	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	B. Braun
Relevant IND(s)	None
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Dual chamber, single-use container: - 500 mg meropenem or 1000 mg meropenem
Indication	Skin and Skin Structure Infections and Intra-abdominal Infections
Dosage and Administration	Adult dose: 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. Adults with Renal Impairment: Mild: No Change Moderate: Recommended dose given every 12 hours Severe: Half of the recommended dose given every 12 hours < 10 mL/min: Half of the recommended dose given every 24 hours Pediatric dose: Pediatric patients weighing over 50 kg should receive the adult dose. There is no recommended dosing for pediatric patients weighing less than 50 kg for this product.

Background

B. Braun submitted a 505(b)(2) New Drug Application (NDA) dated 9/27/13 for Meropenem for Injection and Sodium Chloride for injection in a duplex container. Meropenem is FDA approved for the treatment of complicated skin and skin structure infections at a dose of 500 mg q8h and for complicated intra-abdominal infections at a dose of 1 g q8h. The Sponsor (B. Braun) is seeking approval for 500 mg and 1000 mg meropenem duplex containers. The active ingredient, strength, dosage form, and route of administration are the same between the proposed product and the RLD (MERREM, Meropenem for Injection (NDA 50-706; approved in 1996, manufactured by AstraZeneca).

The proposed product differs from the RLD in the types of diluents that are used (only sodium chloride for the proposed product whereas the RLD is compatible with multiple diluents) and the packaging system (a Duplex container for the proposed product versus a glass vial for the RLD). Table 1 provides a comparison between the proposed product and the RLD.

Table 1: Comparison between the Proposed Product and the RLD

	Generic Drug	Reference Listed Drug
Active Ingredient(s)	Meropenem (Added as Meropenem Trihydrate)	Meropenem (Added as Meropenem Trihydrate)
Inactive Ingredient(s)	Sodium Carbonate (provides (b)(4) mg sodium for 500 mg dose; (b)(4) mg sodium for 1 g dose)	Sodium Carbonate (provides 45.1 mg sodium for 500 mg dose; 90.2 mg sodium for 1 g dose)
Diluent(s)	Sodium Chloride Injection, 0.9%	Sodium Chloride Injection 0.9% Dextrose Injection 5.0% (b)(4)
Packaging System	Duplex® Container	Glass Vials
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	500 mg (as Meropenem) 1 g (as Meropenem)	500 mg (as Meropenem) 1 g (as Meropenem)

The Sponsor intends to rely upon the Agency’s findings for safety and efficacy and information provided in the approved labeling for the RLD, MERREM (meropenem) for Injection. No new clinical pharmacology information was submitted in this application, and the applicant has submitted a request for waiver of the regulatory requirement for bioavailability as outlined in 21 CFR 320.21. Please refer to the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics review for further evaluation of the request for waiver of bioavailability requirements. The scope of this review will be limited to edits on the proposed labeling (see Appendix 1).

Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application, and no new clinical pharmacology information was submitted. Thus, this application is acceptable from a clinical pharmacology standpoint.

Appendix 1: Recommended Labeling Changes

Reviewer comment: For the most part, the submitted label is very similar to the MERREM label. Throughout the label, the Sponsor has replaced the tradename MERREM I.V. with the name of their product – Meropenem for Injection USP and Sodium Chloride Injection USP in addition to minor changes pertaining to product or Sponsor-specific information. The significant changes are the removal of any information pertaining to the bacterial meningitis indication, the removal of information pertaining to the administration of meropenem as a bolus dose (since the proposed product is not intended for bolus administration), and the inclusion of some information describing the limitations of dose adjustment for this product.

It is unclear why the Sponsor removed only the bacterial meningitis indication since all of the pediatric dosing information is weight-based and the following labeling language is present: “To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of Meropenem.” An information request to the company has been sent for clarification purposes. No labeling suggestions or comments will be made on the removal of that information until the information request is addressed. (b) (4)

The relevant portions of the label for clinical pharmacology that have not been covered by one of the above paragraphs are addressed below. The proposed Sponsor text is presented and the Reviewer changes are shown in Track Changes. Sponsor text that is not present in the MERREM label is highlighted.

2.2 Use in Adult Patients with Renal Impairment

Dosage should be reduced in patients with creatinine clearance of 50 mL/min or less. (See dosing table below.)

Dosage should be reduced in renal failure if less than a full dose (1 g or 500 mg) is required and an alternative formulation should be used to avoid risk of overdose.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)⁵ may be used to estimate creatinine clearance.

Males: Creatinine Clearance (mL/min) =

Weight (kg) x (140 - age)

72 x serum creatinine (mg/dL)

Females: 0.85 x above value

Recommended Meropenem for Injection Dosage Schedule for Adult Patients With Renal Impairment

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
> 50	Recommended dose (500 mg cSSSI and 1 g Intra-abdominal)	Every 8 hours
>25-50	Recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours
<10	One-half recommended dose	Every 24 hours

There is inadequate information regarding the use of meropenem for injection in patients on hemodialysis or peritoneal dialysis.

Reviewer comment: Acceptable.

2.3 Use in Pediatric Patients (≥ 3 Months only)

Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX® Container is designed to deliver a 500 mg or 1 g dose of Meropenem. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of Meropenem. Meropenem is not to be used in pediatric patients aged less than three months. There is no experience in pediatric patients with renal impairment. (See dosing table below.) [see *Use in Specific Populations* (8.4)]. Pediatric patients weighing over 50 kg should be administered Meropenem for Injection USP and Sodium Chloride Injection USP at a dose of 500 mg every 8 hours for complicated skin and skin structure infections (b) (4) 1 g every 8 hours for intra-abdominal infections. Meropenem for Injection USP and Sodium Chloride Injection USP should be given as intravenous infusion over approximately 15 to 30 minutes.

Recommended Meropenem for Injection Dosage Schedule for Pediatric Patients With Normal Renal Function

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure	10	500 mg	Every 8 hours
Intra-abdominal	20	1 g	Every 8 hours

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.

There is no experience in pediatric patients with renal impairment.

Reviewer comment: Acceptable.

8.4 Pediatric Use

Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX® Container is designed to deliver a 500 mg or 1 g dose of Meropenem. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of Meropenem. Meropenem is not to be used in pediatric patients aged less than three months. [see *Dosage and Administration* (2.3)].

Use of meropenem for injection in pediatric patients with intra-abdominal infections is supported by evidence from adequate and well-controlled studies with adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. Use of meropenem for injection in pediatric patients with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study with adults and additional data from pediatric pharmacokinetics studies [see *Indications and Usage* (1), *Dosage and Administration* (2.3), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14)].

(b) (4)

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/s/

RYAN P OWEN
06/20/2014

KIMBERLY L BERGMAN
06/20/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202106	Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	September 27, 2013		
Division:	Division of Anti-Infective Products	Team Leader: Angelica Dorantes, PhD	
Applicant:	B. Braun Medical, Inc.	Acting Supervisor: Rik Lostritto, PhD	
Trade Name:	TBD	Date Assigned:	October 1, 2013
Established Name:	Meropenem for Injection USP and Sodium Chloride Injection USP	Date of Review:	May 30, 2014
Indication:	Treatment of skin and skin structure infections and intra-abdominal infections.	Type of Submission: Original New Drug Application – 505(b)(2)	
Dosage form/ strengths	Injection (sterile bulk powder and sterile solution)/ 500 mg and 1 g		
Route of Administration	IV infusion		
Type of Review:	Biowaiver Request		
<u>SUBMISSION:</u>			
<p>The Applicant is seeking approval for a New Drug Application (NDA) for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® container, 0.5 g and 1.0 g strengths, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and is referencing Merrem® IV (meropenem for injection) approved under NDA 50706 on 6/21/1996 (marketed by Astra Zeneca) as the listed drug. The proposed indication is for the treatment of complicated skin and skin structure infections and intra-abdominal infections. The proposed finished drug product consists of Meropenem for Injection (sterile bulk powder) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal which is activated prior to use to constitute the drug powder in the diluent.</p>			

BIOPHARMACEUTIC INFORMATION:

The composition of the proposed drug product is as follows:

Chemical Components of Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container

Drug Chamber	Diluent Chamber	
Meropenem, Dose^a	Sodium Chloride Injection USP	Volume^b
500 mg (as Meropenem, anhydrous)	0.9% w/v	50 mL
1 g (as Meropenem, anhydrous)	0.9% w/v	50 mL

^a Added as Meropenem for Injection (Sterile Bulk) which is a blend of sterile Meropenem Trihydrate USP and sterile Sodium Carbonate USP/NF.

^b The Duplex container system is filled with a nominal volume of (b) (4) mL of diluent to meet the USP minimum volume of 50 mL over the shelf life of the product.

After mixing the contents of the two chambers, the proposed drug product is intended to be administered by IV infusion over a 15 to 30 minutes time period. The Applicant requests a waiver of the requirement for the submission of evidence of in-vivo bioavailability or bioequivalence in accordance with 21 CFR 320.22 (b)(1)(i-ii). The Applicant claims that the proposed drug is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients (b) (4) as a drug product that is the subject of an approved full new drug application (NDA 050706). Therefore, the Applicant claims that the in-vivo bioavailability or bioequivalence of Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container to Merrem® is self-evident based on the approved Merrem® NDA (50706).

BIOPHARMACEUTICS REVIEW:

The Biopharmaceutics review of this NDA will be focused on the evaluation of the information supporting the approvability of the biowaiver request for the proposed drug product. The following table provides a comparison between the proposed drug product and the listed drug:

Item	B. Braun	RLD (AstraZeneca)
1. Name	Meropenem for Injection USP and Sodium Chloride Injection USP	Merrem IV® (Meropenem for Injection) ¹
2. Container	Duplex® (This container system is the same container system used in all of B. Braun drug products approved by the FDA as shown in Table1)	Glass Vial

3. Use	After Constitution with the diluent in the Duplex bag	After Constitution with the diluent and transferred to a suitable IV container for further dilution prior to use
4. Storage	Manufactured State: Controlled Room Temperature, 20-25°C Constituted State: 25°C, 5°C	Manufactured State: Room Temperature, 20-25°C Constituted State: 25°C, 5°C
5. API (blend of Meropenem trihydrate USP and Sodium Carbonate USP/NF)	Meropenem: 500 mg and 1 g Sodium Carbonate, Added as (b) (4) - (b) (4) mg of Sodium Carbonate (which correspond to (b) (4) mg of sodium) per 500 mg of Meropenem (anhydrous equivalent) - (b) (4) mg of Sodium Carbonate (which correspond to (b) (4) mg of sodium) per 1 g of Meropenem (anhydrous equivalent) (This API is the same API used by the RLD, Merrem IV)	Meropenem: 500 mg and 1 g Sodium Carbonate, Added as (b) (4) - (b) (4) mg of Sodium Carbonate (which correspond to 45.1 mg of sodium) per 500 mg of Meropenem (anhydrous equivalent) - (b) (4) mg of Sodium Carbonate (which correspond to 90.2 mg of sodium) per 1 g of Meropenem (anhydrous equivalent)
6. Diluent	0.9% Sodium Chloride Inj., USP	Sodium Chloride Inj. 0.9% Dextrose Inj. 5% (b) (4)
7. Diluent Volume, mL	50mL	10mL for 500mg/vial 20mL for 1g/vial
8. Route of Administration	Intravenous Infusion	Intravenous Infusion Intravenous Bolus
9. Manufacturer	B. Braun Medical, Inc. 500 mg NDC# 0264-3183-11 1 g NDC# 0264-3185-11	AstraZeneca Pharmaceuticals LP 500 mg NDC#0310-0325-20 1 g NDC#0310-0321-30

ASSESSMENT OF THE BIOWAIVER REQUEST:

If the compositions for the formulations of the proposed drug product and the listed (b) (4), then, according to CFR 320.22(b), the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. The drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

It is noted that the volumes of the diluent for the proposed drug product (50 mL) and the listed drug (10 mL or 20 mL) are different. According to the approved label of the listed drug, a solution of up to 50 mg/mL can be administered by bolus injection (5 to 20 mL), or a solution of 1 to 20 mg/mL can be administered by intravenous infusion over 15 to 30 minutes. The proposed drug product is only labeled for administration by intravenous infusion and the drug concentration is either 500 mg/50 mL (10 mg/mL) or 1 g/50 mL (20 mg/mL). Therefore, although the volumes 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. The difference in the container closure system is not expected to change the bioavailability or bioequivalence. Therefore, 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.

RECOMMENDATION:

A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study is granted. From the Biopharmaceutics perspective, NDA 202106 for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container (0.5 and 1.0 g) is recommended for **APPROVAL**.

Signature

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Signature

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
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/s/

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05/30/2014

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06/02/2014