

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202106Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

June 29, 2014

NDA: 202106

Drug Product Name

Proprietary: Meropenem for Injection USP and Sodium Chloride Injection USP in a Duplex Container.

Non-proprietary: meropenem 0.5 g and 1 g.

Review Number: 1

Dates of Submission(s) Covered by this Review

<u>Submit</u>	<u>Received</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
September 27, 2013	September 27, 2013	October 2, 2013	October 4, 2013

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor

Name: B. Braun Medical Inc.

Address: 901 Marcon Boulevard, Allentown, Pennsylvania
18109

Representative: Rebecca Stolarick, Corporate Vice President, RA,
Phone: 610-596-2536.

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** An approval to market meropenem for injection and sodium chloride Injection USP in a DUPLEX (b) (4) container with meropenem considered bioequivalent to the RLD Merrem I.V.
 3. **MANUFACTURING SITE:**
 1. Drug Product Manufacturing site: Facta Farmaceutici S.p.A. Nucleo Industriale S. Atto - S. Nicolò a Tordino 64020 Teramo - Italy
 2. Sterile bulk manufacturing site: (b) (4)
 3. Duplex (u) (4) Container manufacturing site: B. Braun Medical Inc., 2525 McGaw Avenue, Irvine, CA 92614
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

500 mg every 8 hours by intravenous infusion over 15 to 30 minutes for skin and skin structure infections for adult patients and 1g every 8 hours by intravenous infusion over 15 to 30 minutes for intra-abdominal infections for adult patients. (2.1)
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** A penem antibacterial indicated as single agent therapy for the treatment of complicated skin, skin structure infections and complicated intra-abdominal infections.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF Type II (b) (4) & DMF Type V (b) (4)
- C. **REMARKS:** The original NDA 202106 provides for the drug product meropenem (anti-bacterial agent) in a duplex container with Sodium Chloride as a diluent. The active drug product is a bioequivalent of RLD Merrem I.V. This is an electronic submission.

filename: N202106R1

Executive Summary**I. Recommendations**

- A. **Recommendation on Approvability** – Recommend Approval.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – Sterile meropenem bulk powder is manufactured by  (b) (4).
- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. **Contains Potential Precedent Decision(s)** - Yes No

III. Administrative

- A. **Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER
- B. **Endorsement Block** _____
Stephen E. Langille, Ph.D., Sr. Review Microbiologist,
OPS/CDER
- C. **CC Block**
N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE – The sponsor references DMF (b) (4) for information related to Meropenem Sterile Bulk powder manufacturing and testing.

S.2 Manufacture
Meropenum Sterile bulk meropenum Bulk powder is blend of Meropenum Trihydrate USP and Sodium Carbonate USP/NF provided in (b) (4)

S.2.1 Manufacturers
(b) (4)

S.2.2 Description of the Manufacturing Process and Process Controls

Note: The sponsor makes reference to Type II DMF (b) (4) for the manufacturing process for Meropenum Sterile bulk at (b) (4) which includes (b) (4) and (b) (4). In a 3rd DMF (b) (4) Amendment dated January 2013, the DMF holder notifies FDA about the (b) (4)

(b) (4) at the same manufacturing site (b) (4) under the same drug establishment registration number (b) (4). The DMF holder assures that since the approval of (b) (4) [last reviewed and approved by OGD], the manufacturing processes have not been affected due to the transfer of manufacturing process to (b) (4)

(b) (4)

The manufacturing process which including (b) (4) was reviewed and found identical to the previously approved [OGD review 2011] information in DMF (b) (4) and therefore acceptable from regulatory perspective. The information pertaining to (b) (4)

(b) (4) provided in DMF (b) (4) was reviewed for the first time and found acceptable and therefore meets the regulatory

expectations. A formal review of DMF (b) (4) will be provided to the DMF holder.

**S.2.5 Process Validation and/or Evaluation
Sterilization Validation**

The following information has been reviewed in DMF (b) (4) Amendment # 1 received by the Agency on May 5, 2014. The formal review has been addressed to the DMF holder.



ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations for validating the process used for (b) (4) listed above.

S.4 Control of Drug Substance

S.4.1 Specification- The drug substance specifications have not changed since the last approval as indicated in DMF (b) (4)

S.4.2 Analytical Procedures - The Bioburden, Sterility and Bacterial endotoxins test methods are performed according to Eu. Ph. 7Ed. There are no changes to these previously approved test methods and therefore they are acceptable from regulatory perspective.

S.6 Container Closure System



(b) (4)

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations for validating the process used to demonstrate container closure integrity of the subject container.

- S.7 Stability** – Three lots of Meropenem Sterile Bulk Lot 33077185032, Lot 33077185022 and Lot 33077185052 were used in the manufacture of the drug product registration batches and their test results were provided which met the acceptance criteria for sterility and bacterial endotoxins testing.

P. DRUG PRODUCT.

The drug product is packaged in a single use, dual chamber DUPLEX (b) (4) bag consisting of the diluent Sodium Chloride in one chamber and the Meropenem powder in the other. The Meropenem powder is obtained as a sterile powder to be filled in one chamber and sterile diluent manufactured on site and filled in the other chamber. The DUPLEX (b) (4) container closure is manufactured by BBRAUN and is currently approved for several BBRAUN products and therefore will not be reviewed extensively.

P.1 Description of the Composition of the Drug Product

- *Description of drug product* – Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) container is sterile, non-pyrogenic and packaged in a single use, dual chamber container. The finished drug product consists of sterile Meropenem for Injection USP in one chamber and Sodium Chloride Injection USP in the other chamber.
- *Drug product composition* – The labeled composition of the drug product is provided in Table 1 (copied from Table 1, Section 3.2.P.3.2)

Table 1 - Chemical Components and Labeled Composition

Drug Chamber (Meropenem Dose ¹)	Diluent Chamber (Sodium Chloride Injection, 0.9% w/v)
500 mg	(b) (4) mL
1 g	(b) (4) mL

Diluent composition: A quantitative composition is provided in Table 2 (copied from Table 1, Section 3.2.P.3.2).

Table 2 - Quantitative Formulation of the Sodium Chloride Injection USP for the Registration Batches

Component	Target Formulation	Range (Kg)	Range (% Label Claim)
Sodium Chloride 500 mg dose 1 g dose	(b) (4)	(b) (4)	(b) (4)
Total Batch Size, Sodium Chloride Injection	(b) (4)	(b) (4)	(b) (4)

- *Description of container closure system* –The DUPLEX (b) (4) containers are rectangular flexible bags segmented into two consecutive chambers. The chambers are separated by peel able seals which the healthcare professional can rupture at point of use to reconstitute the container's contents. The first container chamber contains a liquid diluent. The second chamber contains a dry powdered antibiotic drug. There is also an empty buffer space separating the drug from the reconstituted solution delivery set port. See DUPLEX (b) (4) Container Closure System under Review Section P.3.3.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –
Containers Leak Test / Visual Inspection: The integrity test methods have been previously approved for several drug products currently manufactured in DUPLEX (b) (4) containers. (b) (4)



(b) (4)



- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

REVIEWER COMMENT – Several drug products have been approved which use the validated process to demonstrate container closure integrity of the subject container and therefore satisfies the regulatory expectations for such process.

(b) (4)



ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product’s microbiological quality throughout its shelf life.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

Facta Farmaceutici S.p.A., declares that the product, **MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP IN THE DUPLEX® CONTAINER**, manufactured in Facta Farmaceutici S.p.A. plant and all the materials used during its production, neither contain nor are produced using material of any animal origins and milk derivatives.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**A. PACKAGE INSERT**

There are no microbiology product quality issues with the drug product label in general or in particular with regard to the reconstitution instructions as presented below:

**ADEQUATE**

REVIEWER COMMENT – The applicant’s labeling of the drug product including the  meet the regulatory expectations.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None

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/s/

VINAYAK B PAWAR
06/30/2014

STEPHEN E LANGILLE
06/30/2014

DIVISION OF ANTI-INFECTIVE PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA 202-106

Date review completed: 6-25-14

Date Company Submitted Document: 9-23-13 CDER Date Received: 9-23-13
Received for Review: 9-23-13 Reviewer: Kerian Grande
Date Assigned: 9-23-13

NAME AND ADDRESS OF SPONSOR

B. Braun Medical Inc.
901 Marcon Boulevard
Allentown, Pennsylvania 18109

CONTACT PERSON

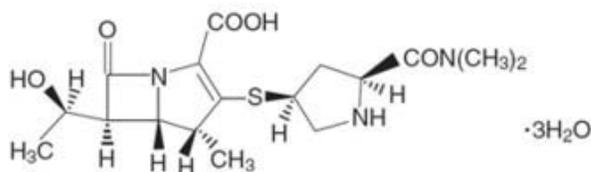
Rebecca Stolarick
Corporate Vice President, Regulatory Affairs
Telephone: (610)-596-2536

DRUG PRODUCT NAME

Proprietary Name: None
Established Name/Code Name(s): Meropenem for Injection USP and Sodium Chloride Injection USP
Chemical Name:
(4*R*,5*S*,6*S*)-3- [[(3*S*,5*S*)-5-(Dimethylcarbamoyl)-3-pyrrolidiny]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Chemical Formulae: C₁₇H₂₅N₃O₅S•3H₂O

Structural Formulae:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

- Complicated skin and skin structure infections (adult patients and pediatric patients requiring the full adult dose only)
- Complicated intra-abdominal infections (adult patients and pediatric patients requiring the full adult dose only)

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NDA 202-106

Date review completed: 6-25-14

**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION,
STRENGTH AND DURATION OF TREATMENT**

Dosage Form: Reconstituted crystalline powder

Route of Administration: Intravenous

Dosage:

- 500 mg every 8 hours by intravenous infusion over 15 to 30 minutes for skin and skin structure infections for adult patients
- 1 g every 8 hours by intravenous infusion over 15 to 30 minutes for intra-abdominal infections for adult patients
- Dosage should be reduced in adult patients with renal impairment

(See proposed package insert for additional information on dosage schedule).

Strength: 500 mg or 1 g dose of Meropenem

Duration of Treatment: No new information provided.

DISPENSED:

Rx

RELATED DOCUMENTS:

NDA 050706

NDA (b) (4)

REMARKS

This is a 505(b)(2) application for meropenem and sodium chloride in a duplex container. The Applicant states that this product is bioequivalent to the RLD, Merrem IV. Strengths, dosing regimen, and route of administration, active and inactive ingredients are as with the RLD. The difference between them is with container (glass vial versus duplex container), and additional diluents used for the RLD. The indication is complicated skin and skin structure infections and complicated intra-abdominal infections.

The indications for both products are the same, except that the merrem RLD is also indicated for bacterial meningitis in pediatric patients greater than or equal to age 3 months. (b) (4)

Therefore, no major changes to the list of organisms, in the Applicant's proposed label, are recommended by this reviewer. *S. pneumoniae*, *H. influenzae*, *N. meningitidis* will continue to remain in the first list, and the associated susceptibility test interpretive criteria will remain in Table 2.

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CONCLUSIONS

From a clinical microbiology perspective, this product may be approved with the recommended labeling changes below. Recommendations include an update to the references. This review is an amendment to the prior clinical microbiology review (5-6-14), in that the current recommendation is to maintain the list of organisms as proposed by the Applicant, because bacterial meningitis will remain in the indications. An amended, Agency-proposed label is below:

Agency's Proposed Label (Only section 12.4 Microbiology and 15, References are shown, this may not be the final draft)

12.4 Microbiology

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*. Bactericidal concentrations (defined as a 3 log₁₀ reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by beta-lactamases, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE).

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Mechanism of Resistance

There are several mechanisms of resistance to carbapenems:

1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) reduced affinity of the target PBPs, 3) increased expression of efflux pump components, and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo-beta-lactamases). Localized clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

Cross-Resistance

Cross-resistance is sometimes observed with isolates resistant to other carbapenems.

Interactions with Other Antibiotics

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Spectrum of Activity

Meropenem has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section (1).

Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates only)

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible isolates only)

Streptococcus pyogenes

Viridans group streptococci

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Date review completed: 6-25-14

Gram-negative bacteria

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Neisseria meningitidis

Pseudomonas aeruginosa

Proteus mirabilis

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Peptostreptococcus species

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90% of the following bacteria have exhibited *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these bacteria **have not been** established in adequate and well-controlled trials.

Gram-positive bacteria

Staphylococcus epidermidis (methicillin-susceptible isolates only)

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Gram-negative bacteria

Aeromonas hydrophila

Campylobacter jejuni

Citrobacter koseri (formerly *diversus*)

Citrobacter freundii

Enterobacter cloacae

Hafnia alvei

Klebsiella oxytoca

Moraxella catarrhalis

Morganella morganii

Pasteurella multocida

Proteus vulgaris

Serratia marcescens

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Bacteroides uniformis

Bacteroides ureolyticus

Bacteroides vulgatus

Clostridium difficile

Clostridium perfringens

Eubacterium lentum

Fusobacterium species

Prevotella bivia

Prevotella intermedia

Prevotella melaninogenica

Porphyromonas asaccharolytica

Propionibacterium acnes

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method. Standardized procedures are based on a dilution method^{1,3} (broth or agar) or equivalent using standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{2,3} and requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-mcg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 2.

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NDA 202-106

Date review completed: 6-25-14

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by a standardized test method.^{2,4} The MIC values obtained should be interpreted according to the criteria provided in Table 2.

Table 2. Susceptibility Interpretive Criteria for Meropenem

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Enterobacteriaceae</i>	≤ 1	2	≥ 4	≥ 23	20-22	≤ 19
<i>Pseudomonas aeruginosa</i> ^a	≤ 2	4	≥ 8	≥ 19	16–18	≤ 15
<i>Haemophilus influenzae</i> ^b	≤ 0.5	—	—	≥ 20	—	—
<i>Neisseria meningitidis</i> ^b	≤ 0.25	—	—	≥ 30	—	—
<i>Streptococcus pneumoniae</i> ^{c,e}	≤ 0.25	0.5	≥ 1	—	—	—
<i>Streptococcus agalactiae</i> and <i>Streptococcus pyogenes</i> ^{b,d,e}	≤ 0.5	—	—	—	—	—
Anaerobes ^f	≤ 4	8	≥ 16	—	—	—

S = Susceptible, I = Intermediate, R = Resistant

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NDA 202-106

Date review completed: 6-25-14

No interpretative criteria have been established for testing enterococci.

Susceptibility of staphylococci to meropenem may be deduced from testing penicillin and either cefoxitin or oxacillin.

- ^a The interpretive criteria for *P. aeruginosa* are based upon the dosing of 1 g every 8 hours
- ^b The current absence of data on resistant isolates precludes defining any category other than “Susceptible”. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.
- ^c For nonmeningitis isolates of *S. pneumoniae* a penicillin MIC of ≤ 0.06 mcg/mL or oxacillin zone ≥ 20 mm can predict susceptibility to meropenem. MIC testing should be performed on isolates that do not test as susceptible by either of these methods, and on all meningitis *S. pneumoniae* isolates.
- ^d Viridans group streptococci should be tested for meropenem susceptibility using an MIC method and results should be reported using the interpretive criteria listed for *S. agalactiae* and *S. pyogenes*.
- ^e Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci
- ^f MIC values using either Brucella blood or Wilkins Chalgren agar (former reference medium) are considered equivalent, based upon published *in vitro* literature and a multicenter collaborative trial for these antimicrobial agents. Broth microdilution is only recommended for testing the *B. fragilis* group. MIC values for agar or broth microdilution are considered equivalent for that group.

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical

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applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard meropenem powder should provide the following range of values noted in Table 3.

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Date review completed: 6-25-14

Table 3. Acceptable Quality Control Ranges for Meropenem

QC Strain	Minimum Inhibitory Concentrations (MICs = mcg/mL)	Disk Diffusion (Zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC® 29213	0.03-0.12	—
<i>Staphylococcus aureus</i> ATCC® 25923	—	29–37
<i>Streptococcus pneumoniae</i> ATCC® 49619	0.06-0.25	28–35
<i>Enterococcus faecalis</i> ATCC® 29212	2–8	
<i>Escherichia coli</i> ATCC® 25922	0.008-0.06	28–34
<i>Haemophilus influenzae</i> ATCC® 49766	0.03-0.12	
<i>Haemophilus influenzae</i> ATCC® 49247	—	20–28
<i>Pseudomonas aeruginosa</i> ATCC® 27853	0.25-1	27–33
<i>Bacteroides fragilis</i> ¹ ATCC® 25285	0.03–0.25	
<i>Bacteroides thetaiotaomicron</i> ¹	0.125-0.5	

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ATCC® 29741		
<i>Eubacterium lentum</i> ¹ ATCC® 43055	0.125-1	
<i>Clostridium difficile</i> ¹ ATCC® 700057	0.5-4	

1. Using the Reference Agar Dilution procedure.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard -Ninth Edition*. CLSI document M07-A (b) (4) Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4)
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A (b) (4) Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4)
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty- (b) (4) Informational Supplement*, CLSI document M100-S2 (b) (4), Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4)
4. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard -Eight Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania (b) (4) 19087 USA, 2012.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31-41.

DIVISION OF ANTI-INFECTIVE PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA 202-106

Date review completed: 6-25-14

Kerian Grande Roche, Ph.D.
Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader
6 May 2014

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

/s/

KERIAN K GRANDE ROCHE
06/27/2014

KERRY SNOW
06/27/2014

DIVISION OF ANTI-INFECTIVE PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA 202-106

Date review completed: 5-6-14

Date Company Submitted Document: 9-23-13 CDER Date Received: 9-23-13
Received for Review: 9-23-13 Reviewer: Kerian Grande
Date Assigned: 9-23-13

NAME AND ADDRESS OF SPONSOR

B. Braun Medical Inc.
901 Marcon Boulevard
Allentown, Pennsylvania 18109

CONTACT PERSON

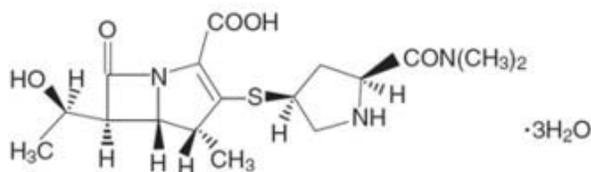
Rebecca Stolarick
Corporate Vice President, Regulatory Affairs
Telephone: (610)-596-2536

DRUG PRODUCT NAME

Proprietary Name: None
Established Name/Code Name(s): Meropenem for Injection USP and Sodium Chloride Injection USP
Chemical Name:
(4*R*,5*S*,6*S*)-3- [[[(3*S*,5*S*)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Chemical Formulae: C₁₇H₂₅N₃O₅S•3H₂O

Structural Formulae:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

- Complicated skin and skin structure infections (adult patients and pediatric patients requiring the full adult dose only)
- Complicated intra-abdominal infections (adult patients and pediatric patients requiring the full adult dose only)

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CLINICAL MICROBIOLOGY REVIEW

NDA 202-106

Date review completed: 5-6-14

**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION,
STRENGTH AND DURATION OF TREATMENT**

Dosage Form: Reconstituted crystalline powder

Route of Administration: Intravenous

Dosage:

- 500 mg every 8 hours by intravenous infusion over 15 to 30 minutes for skin and skin structure infections for adult patients
- 1 g every 8 hours by intravenous infusion over 15 to 30 minutes for intra-abdominal infections for adult patients
- Dosage should be reduced in adult patients with renal impairment

(See proposed package insert for additional information on dosage schedule).

Strength: 500 mg or 1 g dose of Meropenem

Duration of Treatment: No new information provided.

DISPENSED:

Rx

RELATED DOCUMENTS:

NDA 050706

NDA (b) (4)

REMARKS

This is a 505(b)(2) application for meropenem and sodium chloride in a duplex container. The Applicant states that this product is bioequivalent to the RLD, Merrem IV. Strengths, dosing regimen, and route of administration, active and inactive ingredients are as with the RLD. The difference between them is with container (glass vial versus duplex container), and additional diluents used for the RLD. The indication is complicated skin and skin structure infections and complicated intra-abdominal infections.

The indications for both products are the same except that the merrem RLD is also indicated for bacterial meningitis in pediatric patients less than or equal to age 3 months.

(b) (4)
there are no changes proposed by the Applicant to the lists of organisms. *S. pneumoniae*, *H. influenzae*, *N. meningitidis* still remain in the first list.

CONCLUSIONS

From a clinical microbiology perspective, this product may be approved with the recommended labeling changes below. Major recommendations include and update to the

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references, and the removal of the organisms from the lists that are associated with bacterial meningitis, since bacterial meningitis is no longer indicated.

Agency's Proposed Label (Only section 12.4 Microbiology and 15, References are shown, this may not be the final draft)

12.4 Microbiology

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*. Bactericidal concentrations (defined as a 3 log₁₀ reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by beta-lactamases, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE).

Mechanism of Resistance

There are several mechanisms of resistance to carbapenems:

1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) reduced affinity of the target PBPs, 3) increased expression of efflux pump components, and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo-beta-lactamases). Localized clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

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Cross-Resistance

Cross-resistance is sometimes observed with isolates resistant to other carbapenems.

Interactions with Other Antibiotics

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Spectrum of Activity

Meropenem has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section (1).

Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates only)

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus agalactiae

~~*Streptococcus pneumoniae* (penicillin-susceptible isolates only)~~

Streptococcus pyogenes

~~Viridans group streptococci~~ (b) (4)

Gram-negative bacteria

Escherichia coli

~~*Haemophilus influenzae*~~

Klebsiella pneumoniae

~~*Neisseria meningitidis*~~

Pseudomonas aeruginosa

Proteus mirabilis

Anaerobic bacteria

Bacteroides fragilis

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Bacteroides thetaiotaomicron

Peptostreptococcus species

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90% of the following bacteria have exhibited *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these bacteria **have not been** established in adequate and well-controlled trials.

Gram-positive bacteria

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Gram-negative bacteria

Aeromonas hydrophila

Campylobacter jejuni

Citrobacter koseri (formerly *diversus*)

Citrobacter freundii

Enterobacter cloacae

Hafnia alvei

Klebsiella oxytoca

Moraxella catarrhalis

Morganella morganii

Pasteurella multocida

Proteus vulgaris

Serratia marcescens

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Bacteroides uniformis

Bacteroides ureolyticus

Bacteroides vulgatus

Clostridium difficile

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Clostridium perfringens

Eubacterium lentum

Fusobacterium species

Prevotella bivia

Prevotella intermedia

Prevotella melaninogenica

Porphyromonas asaccharolytica

Propionibacterium acnes

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method. Standardized procedures are based on a dilution method^{1,3} (broth or agar) or equivalent using standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{2,3} and

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requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-mcg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 2.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by a standardized test method.^{2,4} The MIC values obtained should be interpreted according to the criteria provided in Table 2.

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Table 2. Susceptibility Interpretive Criteria for Meropenem

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Enterobacteriaceae</i> ^a	≤ 1	2	≥ 4	≥ 23	20-22	≤ 19
<i>Pseudomonas aeruginosa</i> ^a	≤ 2	4	≥ 8	≥ 19	16–18	≤ 15
<i>Haemophilus influenzae</i> ^b	≤ 0.5	—	—	≥ 20	—	—
<i>Neisseria meningitidis</i> ^b	≤ 0.25	—	—	≥ 30	—	—
<i>Streptococcus pneumoniae</i> ^{e,e}	≤ 0.25	0.5	≥ 1	—	—	—
<i>Streptococcus agalactiae</i> and <i>Streptococcus pyogenes</i> ^{b,c,d}	≤ 0.5	—	—	—	—	—
Anaerobes ^e	≤ 4	8	≥ 16	—	—	—

S = Susceptible, I = Intermediate, R = Resistant

No interpretative criteria have been established for testing enterococci.

Susceptibility of staphylococci to meropenem may be deduced from testing penicillin and either cefoxitin or oxacillin.

^a The interpretive criteria for *Enterobacteriaceae* and *P. aeruginosa* are based upon the dosing of 1 g every 8 hours

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^b The current absence of data on resistant isolates precludes defining any category other than “Susceptible”. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

~~^e For nonmeningitis isolates of *S. pneumoniae* a penicillin MIC of ≤ 0.06 mcg/mL or oxacillin zone ≥ 20 mm can predict susceptibility to meropenem. MIC testing should be performed on isolates that do not test as susceptible by either of these methods, and on all meningitis *S. pneumoniae* isolates.~~

~~^{dc} Viridans group streptococci~~ should be tested for meropenem susceptibility using an MIC method and results should be reported using the interpretive criteria listed for *S. agalactiae* and *S. pyogenes*.

^d Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci

^e MIC values using either Brucella blood or Wilkins Chalgren agar (former reference medium) are considered equivalent, based upon published *in vitro* literature and a multicenter collaborative trial for these antimicrobial agents. Broth microdilution is only recommended for testing the *B. fragilis* group. MIC values for agar or broth microdilution are considered equivalent for that group.

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

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Quality Control

Standardized susceptibility test procedures require the use of quality controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard meropenem powder should provide the following range of values noted in Table 3.

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Table 3. Acceptable Quality Control Ranges for Meropenem

QC Strain	Minimum Inhibitory Concentrations (MICs = mcg/mL)	Disk Diffusion (Zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC® 29213	0.03-0.12	—
<i>Staphylococcus aureus</i> ATCC® 25923	—	29–37
<i>Streptococcus pneumoniae</i> ATCC® 49619	0.06-0.25	28–35
<i>Enterococcus faecalis</i> ATCC® 29212	2–8	
<i>Escherichia coli</i> ATCC® 25922	0.008-0.06	28–34
<i>Haemophilus influenzae</i> ATCC® 49766	0.03-0.12	
<i>Haemophilus influenzae</i> ATCC® 49247	—	20–28
<i>Pseudomonas aeruginosa</i> ATCC® 27853	0.25-1	27–33
<i>Bacteroides fragilis</i> ¹ ATCC® 25285	0.03–0.25	
<i>Bacteroides thetaiotaomicron</i> ¹	0.125-0.5	

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ATCC® 29741		
<i>Eubacterium lentum</i> ¹ ATCC® 43055	0.125-1	
<i>Clostridium difficile</i> ¹ ATCC® 700057	0.5-4	

1. Using the Reference Agar Dilution procedure.

15 REFERENCES

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2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard –* (b) (4) (b) (4) CLSI document M02-A (b) (4) Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4)
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4. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard -Eight Edition.* CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania (b) (4) 19087 USA, 2012.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41.

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Kerian Grande Roche, Ph.D.
Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader
6 May 2014

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/s/

KERIAN K GRANDE ROCHE
05/14/2014

KERRY SNOW
05/14/2014