DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Nicholas J. Troise
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals, LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

RE: NDA #50-706
Merrem® I.V. (meropenem for injection)
MACMIS ID #12005

Dear Mr. Troise:

This letter concerns AstraZeneca Pharmaceuticals LP's (AstraZeneca) dissemination of a promotional sales aid (206578) entitled "TRACKING ANTIMICROBIAL RESISTANCE," and a promotional banner (209017) with the claim "Attacking the Tide of Resistance," for Merrem I.V. (meropenem for injection). The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds these promotional materials in violation of the Federal Food, Drug, and Cosmetic Act and its applicable regulations because they make unsubstantiated claims about the efficacy of Merrem I.V. in the treatment of resistant pathogens.

Background

On June 21, 1996, Merrem I.V., a carbapenem antibiotic, was approved as single agent therapy for the treatment of intra-abdominal infections[1] and bacterial meningitis[2] when caused by susceptible strains of the designated microorganisms. The drug has not been approved to treat conditions caused by resistant pathogens.

Promotion for Unapproved Use/ Reliance on In Vitro Data

Promotional materials are false and misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. See 21 U.S.C. §§ 321(n) and 352(a). The promotional materials identified above promote Merrem I.V. for unapproved uses based on *in vitro* data. Cf. 21 C.F.R. § 202.1(e)(6)(vii). Specifically, we object to the following:

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[1] Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron*, and *Peptostreptococcus* species.

[2] Bacterial meningitis (pediatric patients ≥ 3 months only) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (β-lactamase and non-β-lactamase-producing strains), and *Neisseria meningitidis.*

Sales Aid

In your sales aid you present a chart featuring the prominent header "MIC and Susceptibility Data for ESBL-producing *K pneumoniae.*" Additionally, the accompanying chart presents a comparison of the *in vitro* MIC concentrations of numerous antibiotics versus ESBL-producing (Extended Spectrum ß-Lactamase) *K. pneumoniae* to suggest that Merrem I.V. is the only antibiotic that demonstrates the lowest MICs while maintaining susceptibility for ESBL-producing *K. pneumoniae* as the inoculum concentration is increased (i.e., 10^5 CFU/mL increased to 10^7 CFU/mL). This presentation suggests that Merrem I.V. is effective for the treatment of ESBL-producing *K. pneumoniae.* FDA is not aware of substantial evidence or substantial clinical experience that Merrem I.V. is efficacious versus ESBL-producing pathogens. The data you cite to support this claim are derived from a study[3] of 18 *in vitro* bacterial isolates which, although clinical isolates, were not obtained from patients treated with Merrem. These data are inadequate to support any conclusions about the efficacy of Merrem I.V. compared to other antibiotics for the treatment of ESBL-producing *K. pneumoniae*.

Similarly, you present claims such as the headline "A broad spectrum of activity makes it an excellent choice for: Newly Resistant Pathogens, ESBLs…," and such other claims as "In the United States, MERREM I.V. consistently shows high activity against all ESBL-producing strains." These claims throughout your sales aid presented in conjunction with frequent references to antimicrobial resistance and discussions of *in vitro* sensitivity patterns suggest that Merrem I.V. is effective against ESBL producing organisms and other "resistant pathogens" in patients. FDA is not aware of substantial evidence or substantial clinical experience to support these claims.

The Pfaller study[4] cited in your sales aid fails to provide substantial evidence to support claims that Merrem I.V. is effective versus ESBL-producing bacterial strains and resistant pathogens because the data are not from adequate and well-controlled clinical trials. The data are taken from the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection), a global resistance surveillance program that compares the activity of meropenem over time with other agents in medical centers that are actively prescribing meropenem. However, the data are based on *in vitro* activity rather than evidence from clinical studies. *In vitro* data are not an adequate basis on which to accurately predict the clinical effectiveness of an antimicrobial agent. Cf. 21 C.F.R. 202.1(e)(6)(vii). Such data are properly used in conjunction with clinical data to guide therapy and do not serve as a definitive indicator of clinical effectiveness. The disclaimer, "*in vitro* activity does not necessarily correlate with *in vivo* effectiveness," in small print on two of the eight pages does not correct the overwhelmingly misleading suggestion that the *in vitro* data are from adequate and well-controlled clinical trials and form an adequate basis on which to determine clinical effectiveness.

Additionally, you present claims such as "The National Nosocomial Infection Surveillance System (NNISS) 1999 data report a 32% increase in the incidence of imipenem-resistant *P aeruginosa* among nosocomially infected patients in ICUs---this could prove problematic for clinicians in the future." This is directly followed by the claim "Data from 1999 and 2000 MYSTIC Program show that susceptibility of *P aeruginosa* isolates actually increased between 1999 and 2000 for MERREM I.V. (78% to 84%)." The presentation of these claims implies that Merrem demonstrates superior activity against resistant pathogens because of a more favorable resistance pattern than imipenem. FDA is not

[3] Thomson KS, Moland ES. Cefepime, piperacillin-tazobactam, and the inoculum effect in tests with extended-spectrum β-lactamase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother*. 2001;45:3548-3554.
[4] Pfaller MA, Jones RN, Biedenbach DJ, MYSTIC Program Study Group (USA). Antimicrobial resistance trends in medical centers using carbapenems: Report of 1999 and 2000 results from the MYSTIC Program (USA). *Diagn Microbiol Infect Dis*. 2001;41:177-182.

aware of substantial evidence or substantial clinical experience to support these claims. As stated above, *in vitro* data are not an adequate basis on which to accurately predict the clinical effectiveness of an antimicrobial agent. Furthermore, your claims illustrating the resistance patterns of Merrem and imipenem are not consistent with your cited reference (the Pfaller study). You selectively present statements from the Pfaller study while failing to mention that data from the 1999 and 2000 MYSTIC Program also showed that *P. aeruginosa* had increased susceptibility to imipenem as well as to Merrem.

Promotional Banner

Your promotional banner presents the claim "Attacking the Tide of Resistance." This claim suggests that Merrem I.V. is effective for the treatment of drug-resistant pathogens. As stated above, FDA is not aware of substantial evidence or substantial clinical experience to support this claim of clinical efficacy against resistant pathogens.

Conclusions and Requested Actions

The materials identified above promote Merrem I.V. for unapproved uses, including the treatment of resistant pathogens, based on in *vitro* data. To suggest that Merrem I.V. is effective for the treatment of drug-resistant pathogens may promote inappropriate prescribing of Merrem I.V. for these pathogens. Accordingly, your claims cause Merrem I.V. to be misbranded within the meaning of 21 U.S.C. § 352(a).

The development of resistance to antibiotics is an increasing public health concern and as more and more pathogens become resistant to antibiotics, infections caused by resistant pathogens become more difficult to treat. Inappropriate prescribing and over prescribing of antibiotics are factors that contribute to the development of resistant pathogens, which pose a significant public health concern.

1. You should immediately discontinue use of the sales aid and promotional banner and any other promotional materials for Merrem I.V. that contain the same or similar claims or representations as explained above.

2. Please submit a written response to this letter within 10 business days. Your response should explain how you intend to comply with the above and include a list of all promotional materials with the same or similar claims or representations, with the date on which these materials were discontinued.

You should direct your response to Barbara S. Chong, Pharm.D., BCPS by facsimile at (301) 594-6771, or by mail to the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #12005 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Shannon R. Benedetto, Pharm.D., MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Barbara Chong
10/3/03 01:43:14 PM
Signed for Shannon R. Benedetto

TRACKING ANTIMICROBIAL RESISTANCE

Emerging Trends

Extended Spectrum β-Lactamases (ESBLs)

Pseudomonas aeruginosa

Emerging Trends

ESBLs

P aeruginosa

P aeruginosa . . . a difficult problem

- *P aeruginosa* is recognized as a leading cause of nosocomial infections and is difficult to eradicate because there are few agents that are effective against it[1]
- It also shows a particular propensity for the development of resistance, often against multiple antimicrobials such as ceftazidime, piperacillin, imipenem, and gentamicin[2]
- The SENTRY Antimicrobial Surveillance Program has shown that MERREM I.V. susceptibility rates against *P aeruginosa* isolated from US centers have remained relatively stable over a 3-year period[3]

In vitro activity does not necessarily correlate with in vivo effectiveness.

Trends in Antimicrobial Susceptibility of *P aeruginosa* Isolated From US Centers During 1997, 1998, and 1999 (SENTRY Antimicrobial Surveillance Program)

	Percentage of isolates susceptible		
Antimicrobial agent	1997	1998	1999
β-Lactams			
Aztreonam	67.0	64.7	62.3
Piperacillin	87.9	87.3	83.7
Piperacillin/tazobactam	89.9	89.9	86.6
Ceftazidime	79.5	81.2	78.1
Cefepime	77.7	85.8	83.1
Imipenem	88.0	85.2	80.9
MERREM I.V.	92.4	90.8	90.9
Aminoglycosides			
Amikacin	95.0	94.8	96.6
Tobramycin	91.1	92.7	92.2

—adapted from Gales et al[3]

- MERREM I.V. demonstrated higher susceptibility rates than any other β-lactam; only aminoglycosides exhibited higher activity[3]

- *Citrobacter* spp, *Enterobacter* spp, and *Serratia* spp are all potential producers of AmpC β-lactamases; and resistant strains of *Acinetobacter* spp have been appearing in New York City[2]
- Data from 1999 and 2000 MYSTIC Program show that *Citrobacter* spp remains susceptible to MERREM I.V., imipenem, cefepime, ciprofloxacin, and the aminoglycosides, but susceptibility to piperacillin/tazobactam decreased by 10%[2]
- MERREM I.V., imipenem, cefepime, ciprofloxacin, gentamicin, and tobramycin were the most active agents tested against *Enterobacter* spp[2]
- Only MERREM I.V., imipenem, and tobramycin inhibited more than 70% of *Acinetobacter* spp isolates over the 2-year period; the greatest decrease in activity was seen with piperacillin/tazobactam[2]

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another β-lactam.

MERREM I.V.
meropenem for injection

Please see accompanying full Prescribing Information.

ESBLs . . . an evolving problem

- Increased use of certain antimicrobial agents has contributed to the development of ESBL-producing pathogens, specifically *Klebsiella pneumoniae* and *Escherichia coli*

In vitro activity does not necessarily correlate with in vivo effectiveness.

MIC and Susceptibility Data for ESBL-producing *K pneumoniae*[*]

Inoculum: 10^5 CFU/mL (n=18) and antibiotic	MIC (µg/mL) Range	MIC_{50}	MIC_{90}	% Susceptible
MERREM I.V.	≤0.015-0.12	0.03	0.06	100
Cefotetan	0.06-2	0.25	1	100
Cefotaxime	0.5-64	4	32	67
Ceftazidime	1->1024	256	1024	11
Ceftriaxone	1-128	4	64	56
Cefepime	0.5-16	4	16	89
Aztreonam	0.5->1024	64	512	22
Piperacillin/ tazobactam	2-1024	8	1024	67
Inoculum: 10^7 CFU/mL (n=18) and antibiotic				
MERREM I.V.	0.03-4	0.125	4	100 (6/18)
Cefotetan	0.06-32	2	16	90 (6/18)
Cefotaxime	8->1024	256	>1024	5 (18/18)
Ceftazidime	8->1024	>1024	>1024	5 (6/6)
Ceftriaxone	128->1024	>1024	>1024	0 (18/18)
Cefepime	>128	>128	>128	0 (18/18)
Aztreonam	4->1024	>1024	>1024	11 (9/12)
Piperacillin/ tazobactam	4->1024	1024	>1024	22 (8/14)

—adapted from Thompson and Moland[1]

[*]Susceptibility based on the percentage of strains inhibited at the NCCLS susceptible breakpoint concentration of each agent. (The breakpoints are only validated for the tests with the 10^5 CFU/mL inoculum.)

[†]For the inoculum of 10^7 CFU/mL, in addition to percent susceptibility, the following is shown parenthetically: number of strains showing inoculum effect/number of strains evaluable. (Not all tests were evaluable. For some MICs out of the test range it was impossible to determine if there was an 8-fold increase in MIC.)

- In this in vitro study, MERREM I.V. and cefotetan were the least affected by the inoculum effect,* demonstrating better activity against ESBL-producing species than piperacillin/tazobactam and the fourth-generation cephalosporin, cefepime[3]
- Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) tracks trends in resistance and compares the activity of MERREM I.V. with other agents used in medical centers
- In the United States, MERREM I.V. consistently shows high activity against all ESBL-producing strains[2]
- MERREM I.V. demonstrates potent antibacterial activity even in hospitals with increasing rates of resistance to other extended-spectrum β-lactam agents[2]

*Inoculum effect is defined as an 8-fold or greater MIC increase on testing with a 100-fold–higher inoculum.

ESBLs

P aeruginosa

As with other broad-spectrum antibiotics, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms.

MERREM® I.V.
meropenem for injection

Please see accompanying full Prescribing Information.

Resistance . . . emerging trends

- In the past 2 decades a number of pathogens have demonstrated resistance to commonly used antimicrobials[1]

Emerging Trends in Antibiotic Resistance

Organisms	Resistances
Gram-positive pathogens	
Staphylococci	Penicillin, oxacillin, macrolides
Enterococci	Glycopeptides, penicillins, aminoglycosides
Streptococci	Penicillin, macrolides, some cephalosporins
Corynebacterium spp	Multiple drugs
Bacillus spp	β-Lactams
Gram-negative pathogens	
Haemophilus spp	Penicillins (β-lactamases)
Moraxella catarrhalis	β-Lactams (β-lactamases)
Klebsiella spp	Newer cephalosporins (ESBLs)
Enterobacter spp*	Newer cephalosporins (inducible/derepressed β-lactamases)
Stenotrophomonas maltophilia	Multiple drugs
Neisseria spp	β-Lactams, fluoroquinolones
Acinetobacter spp	Multiple drugs
Pseudomonas spp	Multiple drugs
Bacteroides fragilis group	Clindamycin, cephamycins

*Also Bush-Jacoby-Medeiros group 1 enzyme-producing species such as *Citrobacter freundii*, *Serratia marcescens*, and indole-positive protease.

—adapted from Jones and Pfaller

- The National Nosocomial Infection Surveillance System (NNISS) 1999 data report a 32% increase in the incidence of imipenem-resistant *P aeruginosa* among nosocomially infected patients in ICUs—this could prove problematic for clinicians in the future[1,2]
- Data from 1999 and 2000 MYSTIC Program show that susceptibility of *P aeruginosa* isolates actually increased between 1999 and 2000 for MERREM I.V. (78% to 84%)[3]

Activity of MERREM I.V. and Comparators Against *P aeruginosa* From MYSTIC Program USA

	1999 (n=193)		2000 (n=299)	
Antibiotic	$MIC_{50/90}$	% Susceptible	$MIC_{50/90}$	% Susceptible
MERREM I.V.	**1/16**	78	0.5/8	84
Imipenem	2/16	78	2/16	81
Ceftriaxone	64/64	5	64/64	9
Ceftazidime	4/>16	83	4/>16	83
Cefepime	4/16	79	4/16	81
Piperacillin/tazobactam	8/≥128	89	8/128	86
Ciprofloxacin	0.25/>2	83	0.25/>2	74
Gentamicin	2/8	87	2/8	82
Tobramycin	1/2	93	1/2	92

—adapted from Pfaller et al[3]

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-lactams.

MERREM I.V.
meropenem for injection

Please see accompanying full Prescribing Information.

P aeruginosa

A broad spectrum of activity makes it an excellent choice for:

Newly Resistant Pathogens

ESBLs

P aeruginosa

MERREM I.V. is indicated as single-agent therapy for the treatment of complicated appendicitis and peritonitis and pediatric (≥3 months only) bacterial meningitis when caused by susceptible organisms.

MERREM I.V. is contraindicated in patients with known hypersensitivity to any component of the product, or to other drugs in the same class, or in patients who have demonstrated anaphylactic reactions to β-lactams.

References: 1. Jones RN, Pfaller MA. Bacterial resistance: a worldwide problem. *Diagn Microbiol Infect Dis.* 1998;31:379-388. 2. Pfaller MA, Jones RN, Biedenbach DJ, MYSTIC Program Study Group (USA). Antimicrobial resistance trends in medical centers using carbapenems: report of 1999 and 2000 results from the MYSTIC Program (USA). *Diagn Microbiol Infect Dis.* 2001;41:177-182. 3. Thomson KS, Moland ES. Cefepime, piperacillin-tazobactam, and the inoculum effect in tests with extended-spectrum β-lactamase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother.* 2001;45:3548-3554. 4. Harris AD, Smith D, Johnson JA, Bradham DD, Roghmann M-C. Risk factors for imipenem-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Clin Infect Dis.* 2002;34:340-345. 5. Gales AC, Jones RN, Turnidge J, Rennie R, Ramphal R. Characterization of *Pseudomonas aeruginosa* isolates: occurrence rates, antimicrobial susceptibility patterns, and molecular typing in the global SENTRY antimicrobial surveillance program, 1997-1999. *Clin Infect Dis.* 2001;32(suppl 2):S146-S155. 6. Data on file. NNISS 1999 report. AstraZeneca Pharmaceuticals LP, Wilmington, Delaware.

AstraZeneca

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1800 Concord Pike PO Box 8437
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MERREM® I.V.
meropenem for injection

Please see accompanying full Prescribing Information.

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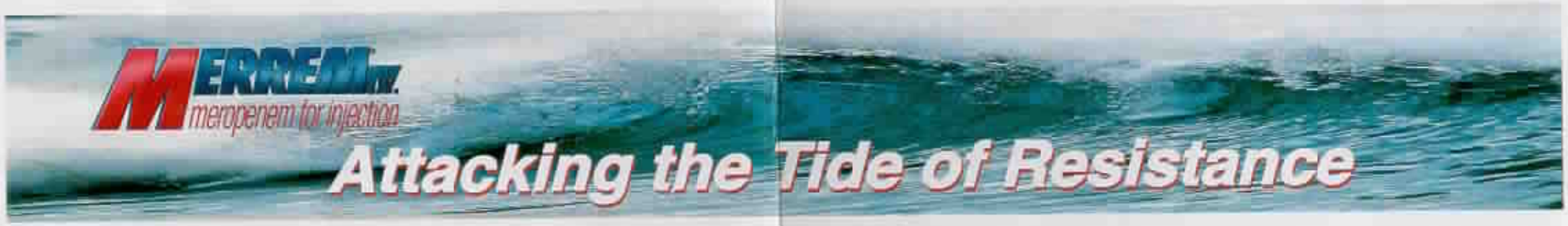

Option - A

ELEVATION

30ft L. x 4ft H. Banner