Drug Monograph

Drug/Drug Class:	**Zemdri™ (plazomicin) injection / Aminoglycoside Antibacterial**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Zemdri™ is available in a single dose vial containing 500 mg plazomicin per 10 ml solution. Manufactured for: Achaogen, Inc., South San Francisco, CA 94080
Summary of Findings:	Zemdri™ was evaluated in a multinational, double-blind, noninferiority clinical trial in which 609 adults hospitalized with complicated UTI (including pyelonephritis) were randomized to receive Zemdri™ or meropenem. In the clinical trial, Zemdri™ demonstrated efficacy for composite cure at Day 5 and the Test of Cure visit in 88% and 81.7% of patients respectively.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☐ Appropriate Indications ☒ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Approximately 40% of all nosocomial infections are UTIs, and most are associated with catheters, resulting in over 1 million catheter-associated UTIs in the US each year. Pyelonephritis and complicated UTI most commonly occur by migration of enteric bacteria from the intestinal tract into the urethra and ascensions into the urinary system. Complicated UTI risk is greatest in patients with abnormal voiding and may be suggested by a history of urinary retention, recurrent UTI, or urinary procedures, including stent or catheter placement. Symptoms of pyelonephritis include: costovertebral tenderness, back or flank pain, chills, fever, nausea, and vomiting.

Dosage Form [1]

Zemdri™ is available in a single dose vial containing 500 mg plazomicin per 10 ml solution.

Manufacturer [1]

Manufactured for: Achaogen, Inc., South San Francisco, CA 94080

Indication(s) [1]

Zemdri™ is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis cause by the following susceptible microorganism(s): *Escherichia coli, Klebsiella pneumonia, Proteus mirabilis*, and *Enterobacter cloacae*.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Zemdri™ is an aminoglycoside that acts by binding to bacterial 30S ribosomal subunit, thereby inhibiting protein synthesis.

Pharmacokinetics:

	Zemdri™
Protein Binding	20%
Excretion	97.5% kidney; 0.2% feces
Clearance	5.1 L/hour
Half-life	3.5 hours

Clinical Trials:

STUDY DESIGN	Multinational, double-blind, noninferiority clinical trial (n=609)
INCLUSION CRITERIA	Patients hospitalized with cUTI (including pyelonephritis). Included all patients who received study medication and had at least 1 baseline uropathogen
EXCLUSION CRITERIA	Organisms resistant to study drugs
TREATMENT REGIMEN	Patients were randomized to receive Zemdri™ (15 mg/kg IV once daily as a 30-minute infusion) or meropenem (1 g intravenously every 8 hours as a 30-minute infusion). Switch to an oral antibacterial drug, such as levofloxacin, was allowed after a minimum of 4 and maximum of 7 days of IV therapy for a total of 7 to 10 days of treatment.
RESULTS	Efficacy was established based on composite cure at Day 5 and the Test of Cure visit. Composite cure at Day 5 was defined as resolution or improvement of clinical cUTI symptoms and a microbiological outcome of eradication. Composite cure at the Test of Cure visit was defined as resolution of clinical cUTI symptoms and a microbiological outcome of eradication. In the Zemdri™ group, 88% of patients had composite cure at Day 5 compared to 91.4% of patients receiving meropenem. 81.7% of patients receiving Zemdri™ had a composite cure at the Test of Cure visit compared to 70.1% of patients receiving meropenem. There were 52 baseline Enterobacteriaceae isolated in 27% of patients in the Zemdri™ group that were non-susceptible to gentamicin, or tobramycin or both. All of these isolates were susceptible to plazomicin and all but on was susceptible to amikacin. In this population, 89.4% of patients achieved microbiological eradication at the Test of Cure visit compared to 75.5% of patients receiving meropenem.
SAFETY	The most frequent adverse events occurring in >2% of patients receiving Zemdri were decreased renal function, diarrhea, and hypertension.

Contraindications [(1)]

- Known hypersensitivity to any aminoglycoside

Warnings and Precautions [(1)]

- Nephrotoxicity has been reported with the use of Zemdri™. Most serum creatinine increases were ≤ 1 mg/dl above baseline and reversible
- Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported

- Aminoglycosides have been associated with exacerbation of muscle weakness in patients receiving concomitant neuromuscular blocking agents
- Aminoglycosides can cause fetal harm when administered to a pregnant woman
- Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving aminoglycoside antibacterial drugs.
- *Clostridium difficile*-assocated diarrhea has been reported for nearly all systemic antibacterial drugs.
- Prescribing Zemdri™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adverse Effects [(1)]

Most common, ≥ 1%	Zemdri™ (n=303) **%**	Meropenem (n=301) %
Decreased Renal Function	3.6	1.3
Diarrhea	2.3	1.7
Hypertension	2.3	2.3
Headache	1.3	3
Nausea	1.3	1.3
Vomiting	1.3	1
Hypotension	1	0.7

Drug Interactions [(1)]

- There are no known significant drug interactions.

Dosage and Administration [(1)]

The recommended dosage regimen of Zemdri™ is 15 mg/kg administered every 24 hours by intravenous infusion over 30 minutes in patients 18 years of age or older and with creatinine clearance greater than or equal to 90 ml/min. The duration of therapy should be guided by the severity of infection and the patient's clinical status for up to 7 days.

Cost

Generic Name	**Brand Name**	**Manufacturer**	**Dose**	**Cost/vial**
Plazomycin	Zemdri™	Achaogen	500 mg/10 ml	$315**
Meropenem	N/A	Fresenius Kabi	500 mg	$6.18*

* Maximum Allowable Cost

** Wholesale Acquisition Cost

Conclusion

Zemdri™ is a novel aminoglycoside antibiotic indicated for the treatment of complicated urinary tract infections, including pyelonephritis, caused by certain Enterobacteriaceae in patients who have limited or no alternative treatment options. Zemdri™ is an intravenous infusion, administered once daily that has demonstrated evidence of efficacy in treating multi-drug resistant bacteria, including those resistant to other aminoglycosides. Zemdri™ should be reserved for those patients that are resistance to alternative antibiotic therapies and are proven or strongly suspected to be caused by susceptible microorganisms in order to reduce the development of drug-resistant bacteria.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Zemdri™ (plazomicin). Retrieved 11/23/2018 from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0b82ffed-27f4-4f5c-8135-670c148f0e12&audience=consumer
2) Zemdri (plazomicin). IPD Analytics Rx Insights_New Drug Approval Review_Zemdri_07 2018.pdf

Prepared by: Luke Boehmer PharmD

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