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Oritavancin for acute bacterial skin and skin structure infection

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Abstract

Introduction—Inpatient treatment of acute bacterial skin and skin structure infections (ABSSSI) exerts a significant economic burden on the healthcare system. Oritavancin is a concentration-dependent, rapidly bactericidal agent approved for the treatment of ABSSSI. Its prolonged half-life with one-time intravenous (IV) dosing offers a potential solution to this burden. In addition, oritavancin represents an alternative therapy for *Streptococci* and multidrug resistant gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Animal models have also shown promising results with oritavancin for other disease states including those that require long courses of IV therapy.

Areas covered—This review covers oritavancin's basic chemistry, spectrum of activity, pharmacodynamics/ pharmacokinetics, efficacy in clinical trials, and provides expert opinion on future directions. To compose this review, a search of PubMed was performed, and articles written in the English language were selected based on full text availability.

Expert Opinion—If oritavancin is proven to be a cost-effective strategy for outpatient treatment and prevents complications of prolonged IV therapy, it will be sought as an alternative antibiotic therapy for ABSSSI. In addition, further clinical data demonstrating efficacy in gram-positive infections requiring prolonged therapy such as endocarditis and osteomyelitis could support oritavancin's success in the current market.

Keywords

acute bacterial skin and skin structure infection; lipoglycopeptide; oritavancin; *Staphylococcus aureus*

1.0 Introduction

Acute bacterial skin and skin structure infections (ABSSSI) including cellulitis, wound infections, and major cutaneous abscesses, the majority of which are due to gram-positive

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organisms, exert significant economic pressure on the healthcare system^{1–3}. An estimated 750,000 patients per year in the United States are admitted to the hospital for ABSSSI incurring an estimated cost of >6 billion dollars⁴.

Oritavancin is a long acting, concentration-dependent, rapidly bactericidal agent newly approved for use in ABSSSI⁵. It offers a potential solution to alleviate this economic burden with effective, one-time intravenous dosing over 3 hours, eliminating the need for prolonged intravenous (IV) catheters and therapeutic drug monitoring. In addition, oritavancin dosing does not have to be adjusted based on age, weight, or mild to moderate hepatic or renal dysfunction. This review focuses on the chemistry, spectrum of activity, pharmacodynamics/pharmacokinetics (PD/PK), safety and efficacy in clinical trials, and future directions in the use of oritavancin.

2.0 Overview of the market

As demonstrated in clinical trials of ABSSSI, the majority of skin and soft tissue infections are due to *S. aureus*, and empiric therapy is often directed against methicillin-resistant *S. aureus* (MRSA). Historically the first choice for MRSA infection, vancomycin requires dose-adjustment for renal insufficiency and close therapeutic monitoring to achieve a narrow window of efficacy without inducing toxicity with supratherapeutic serum levels. With the evolution of *S. aureus* exhibiting reduced⁶ and complete⁷ resistance to vancomycin, alternative therapies are increasingly required. Unfortunately, most alternatives to vancomycin also have important limitations. For example, treatment-emergent resistance to daptomycin has occurred in approximately 5% of patients receiving the drug in the registration trial⁸ and has been described to occur in up to 60% of specific high-risk populations⁹.

Newer antibiotics for the treatment of ABSSSI with anti-MRSA activity include ceftaroline, tedizolid, telavancin, dalbavancin, and oritavancin. In clinical trials, ceftaroline has demonstrated non-inferiority to vancomycin in treatment of ABSSSI, but its dosing regimen is 2 to 3 times per day¹⁰. Tedizolid has superior pharmacokinetics, potentially reduced toxicity compared to linezolid, and activity against *S. aureus* isolates with the *cfr*-element (which confers linezolid resistance)^{11, 12}. Compared to linezolid's twice daily dosing for 7–10 days, tedizolid is taken once daily for 6 days potentially enhancing compliance. Telavancin is a lipoglycopeptide that allows daily dosing but requires monitoring of serum creatinine due to associated nephrotoxicity^{13–15}. Dalbavancin is another semi-synthetic lipoglycopeptide that is given as a single 1000mg IV dose initially followed by a single 500mg dose 1 week later, has excellent coverage of MRSA and MSSA, but is inactive against *vanA* strains of vancomycin-resistant *Enterococcus* (VRE)¹⁶.

3.0 Introduction to the compound

3.1 Chemistry

Oritavancin, a semi-synthetic lipoglycopeptide, was first described in 1996 as a derivative from the natural product, chloroeremomycin, with addition of a 4'-chlorobiphenylmethyl group¹⁷. Oritavancin has three mechanisms of action: 1) inhibition of the transglycosylation

step of bacterial cell wall biosynthesis by binding the stem peptide of peptidoglycan precursors, 2) inhibition of the transpeptidation, or cross-linking step of cell wall biosynthesis by binding peptide bridging segments of the cell wall, and 3) disruption of bacterial membrane integrity leading to depolarization, increased membrane permeability, and cell death¹⁸.

Oritavancin demonstrates excellent in vitro activity (MIC) against *S. aureus*, notably methicillin-resistant *S. aureus*, Vancomycin-intermediate *S. aureus* (VISA), and Vancomycin-resistant *S. aureus* (VRSA) strains^{19, 20}. Lin, et al. (2014) tested Oritavancin's in vitro activity against 203 MRSA isolates of community and healthcare-acquired origin. The investigators report Oritavancin MIC₅₀ and MIC₉₀ of 0.12 and 0.25, respectively, versus 169 isolates of community- and hospital-associated MRSA. Oritavancin MIC ranges were 0.12–0.5 µg/mL versus 5 Heterogeneous Vancomycin-intermediate *S. aureus* (hVISA) strains, 0.5–2 µg/mL versus 5 VISA strains, and 0.12–1 µg/mL versus 5 VRSA strains. Of note, among VISA and VRSA isolates, only three possessed an oritavancin MIC >1 µg/mL.

Oritavancin has also demonstrated activity against coagulase-negative *Staphylococci* (CoNS), *Streptococci*, and other gram-positive organisms including vancomycin-resistant *Enterococci*^{21, 22} (Table 1).

3.2 Pharmacodynamics

Oritavancin's pharmacodynamic (PD) profile was studied in vitro and in vivo models. In animal models, its antimicrobial activity correlated with the ratio of the area under the concentration-time curve to MIC (AUC/MIC)²³. Oritavancin's concentration-dependent killing was determined from in vitro time-kill studies in which increasing concentrations of oritavancin led to progressively greater rate and extent of killing²⁴.

Belley et al. (2013) compared the in vitro PD based on population PD/PK of simulated dosing regimens of a single infusion of oritavancin 1200mg IV to daptomycin and vancomycin and noted that the single dose of oritavancin exerted rapidly bactericidal activity within the first 2–3 hours of infusion against all 3 MRSA isolates tested²⁵. The mean decreases in bacterial viability after oritavancin administration were significantly greater at 2 hours compared to vancomycin for all 3 MRSA strains including an hVISA isolate (oritavancin vs. vancomycin [log CFU/mL ± standard deviation (SD)]: -4.3 ± 0.1 vs. -0.6 ± 0.3 for MRSA NRS123; -3.7 ± 0.4 vs. -0.2 ± 0.1 for MRSA ATCC 33591; -4.0 ± 0.1 vs. -0.1 ± 0.1 for MRSA-hVISA 1561603). Oritavancin administration resulted in significantly greater mean decreases in bacterial viability at 24 hours compared to daptomycin and vancomycin respectively (-3.3 ± 0.7 vs. -4.2 ± 0.0 vs. -3.2 ± 0.3 for MRSA NRS123, -4.1 ± 0.0 vs. -2.2 ± 0.5 vs. -3.2 ± 0.8 for MRSA ATCC 33591, and -4.1 ± 0.1 vs. -3.1 ± 0.6 vs. -2.7 ± 0.2 for MRSA-hVISA 1561603).

3.3 Pharmacokinetics and metabolism

The pharmacokinetics from Phase II and Phase III studies fit into a dose-linear, three-compartment model with two distributional half-life's ($T_{1/2}$'s), alpha and beta, of 2.29 and 13.4 hours respectively and a terminal elimination $T_{1/2}$ (gamma) of 245 hours, which is >10

days^{25–27}. The terminal half-life is prolonged due to oritavancin's increased protein binding, up to 85–90%, its lipophilic side chain, and its volume of distribution approaching 110 L with slow release from tissue absorption sites. Due to the prolonged terminal $T_{1/2}$, recent clinical trials have utilized a one-time dosing strategy of 1200mg IV^{28, 29}. To support this strategy, in vitro PD/PK modeling demonstrated that oritavancin single 1200mg IV infusion is as effective over 72 hours as daptomycin 6 mg/kg IV daily and vancomycin 1g IV twice daily²⁵.

Oritavancin is not metabolized and is excreted slowly and unchanged in urine (<5%) and feces (<1%) up to 7 days after dosing³⁰. Although no dose adjustment is recommended for patients with renal failure, the pharmacokinetics of oritavancin in severe renal impairment, defined by a creatinine clearance less than 30, or on hemodialysis has not been studied. Clearly further clinical studies are needed before initiating oritavancin therapy in this group of patients.

4.0 Clinical efficacy

4.1 Phase I studies

A Phase I open-label, non-controlled, dose escalation study of oritavancin 1200 mg IV in 11 healthy human subjects was performed to evaluate safety and pharmacokinetics of the drug³⁰. Oritavancin was well tolerated without serious safety events. Of note, 5 subjects did experience transient, asymptomatic elevation in liver transaminases without associated elevation in bilirubin. In 3 subjects, liver transaminase elevation peaked at <1.5 times the upper limit of normal (ULN). In a fourth subject, liver transaminases increased <3 times ULN but subsequently declined. In the fifth subject, liver transaminases peaked at 70 days after study initiation with AST of 444 U/L and ALT of 334 U/L but subsequently declined. Of note, this subject did admit to significant alcohol consumption.

4.2 Phase II studies

SIMPLIFI was a Phase II multi-center, randomized, double blind, parallel active-comparator study testing non-inferiority of single (1200 mg IV) or infrequent doses to daily doses of oritavancin for adults with ABSSSI³¹. For infrequent dosing, patients received 800mg IV on day 1 with the option of additional 400mg IV on day 5. Primary efficacy was defined as clinical response at days 21 to 29. With a 15% non-inferiority margin, single dosing was non-inferior to infrequent dosing in efficacy and safety in treating ABSSSI.

Oritavancin has also been studied in an international, multicenter clinical trial evaluating the relationship between microbiologic and clinical response and oritavancin exposure in the treatment of *S. aureus* bacteremia³². Adult patients were randomized to receive either 10–14 days of oritavancin at four different weight-based doses or control (vancomycin or beta-lactam). A total of 86 patients received oritavancin and underwent plasma PK measurements at varying points on day 1 through day 42 ± 7 days. Of these 86 patients, 55 patients were evaluable for microbiologic and clinical responses. Forty-seven patients treated with oritavancin achieved microbiologic success, and 45 patients achieved clinical success. The investigators concluded that there was a positive exposure-response relationship in the treatment of *S. aureus* bacteremia with oritavancin based on PK-PD modeling. However,

since this study was conducted, it was determined oritavancin in vitro potency was being underestimated by approximately 16- to 32-fold in the absence of polysorbate-80 in the MIC assay as discussed in the “Regulatory affairs” section below. Therefore, time above the MIC ($T > MIC$) is not a PK/PD parameter that is presently associated with oritavancin efficacy.

4.3 Phase III studies

SOLO I and SOLO II were large Phase III international, multi-center, randomized, double-blind clinical trials comparing a single dose of oritavancin 1200mg IV to twice daily vancomycin for ABSSSI^{28, 29}. The primary composite endpoint was cessation of spreading or reduction of lesion size measured at 48–72 hours, the absence of fever, and no need for rescue antibiotics. The secondary endpoints were investigator-assessed clinical cure within 7–14 days after treatment cessation and 20% reduction in lesion size 48–72 hours after initiation of antibiotic therapy. Patients were followed for 60 days to evaluate safety and tolerability of oritavancin’s extended terminal $T_{1/2}$. Both trials demonstrated that single dosing of oritavancin was non-inferior (margin of 10%) to vancomycin in a modified-intent-to treat analysis of efficacy.

5.0 Safety and tolerability

To date, over one thousand patients have been enrolled into clinical trials testing safety and efficacy of oritavancin for the treatment of patients with ABSSSI with minimal serious safety reports or trial withdrawal due to intolerability of the drug. In SOLO I, at least one treatment-emergent adverse event (TEAE) occurred in 108 (22.8%) patients in the oritavancin arm compared to 151 (31.4%) in the vancomycin arm, and at least one TEAE leading to discontinuation of study drug in 18 (3.8%) patients in the oritavancin arm versus 28 (5.8%) in the vancomycin arm. Serious TEAE leading to discontinuation of study drug occurred in 3 (0.6%) patients in the oritavancin arm and 3 (0.6%) in the vancomycin arm. In SOLO II, study drug-related TEAE occurred in 109 (21.7%) of patients in the oritavancin arm vs. 128 (25.5%) in the vancomycin arm. TEAE leading to study drug discontinuation occurred in 18 (3.6%) patients in the oritavancin group and 13 (2.6%) in the vancomycin group. Importantly, there was not a notable difference between time of onset and duration of adverse events in patients treated with oritavancin compared to vancomycin in either of the Phase III trials^{28, 29}.

The most commonly reported side effects observed in Phase III SOLO trials were headache, nausea, vomiting, limb and subcutaneous abscess, and diarrhea³³. Transient ALT elevations were also observed, but no cases that met Hy’s law criteria (>3 -fold elevation of AST or ALT above the ULN and total bilirubin >2 -fold above the ULN) were identified. Infusion reactions occurred and included pruritus, urticaria, and flushing but resolved with slowing rate of infusion and were less frequent than with the comparator, vancomycin. Hypersensitivity reactions occurred with median onset of 1.2 days and median duration of reaction of 2.4 days. Rare episodes of leukocytoclastic vasculitis, erythema multiforme, and angioedema were also reported at rates 1.5%. Oritavancin carries a pregnancy category C with safety only demonstrated in animal models. Similarly, safety of oritavancin in nursing mothers has not yet been established.

Although oritavancin does not have direct effect on the coagulation cascade, it has weak activity on the cytochrome P450 system. Thus, oritavancin co-administration with warfarin may result in higher exposure to warfarin and increased risk of bleeding. In addition, oritavancin artificially prolongs PT and PTT tests for up to 48 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests and INR tests for up to 24 hours" after "PT" since oritavancin's in vitro effect on PT and INR is not longer than 24 hours. Therefore, use of unfractionated heparin is contra-indicated within 48 hours of oritavancin infusion.

6.0 Regulatory affairs

Oritavancin's development was slow to progress due to succession of ownership among pharmaceutical companies and an initial overestimation of *S. aureus* and enterococci MICs. Eli Lilly synthesized the drug in 1994 with the designation LY333328, but the compound was acquired by Intermune Inc. in 2002, followed by Targanta Therapeutics Corporation in 2006, and finally by the Medicines Companies in 2009^{17, 23}. Initially, oritavancin's MICs to methicillin-susceptible *S. aureus* (MSSA), MRSA, and Enterococci were substantially over-estimated as investigators did not account for oritavancin's non-specific binding losses through sticking to the walls of the test tubes during MIC assays. However, in 2008, work by Arhin et al. confirmed a 16 to 32-fold overestimation of MIC against staphylococci and enterococci³⁴.

The first FDA drug application for oritavancin, submitted in 2008, was unsuccessful leading to the request for another Phase III trial and further evaluation of the effects of the drug on macrophage function³⁵. Concerns about the potential of oritavancin decreasing effectiveness of macrophage function arose from the observation of its marked accumulation in lysosomes of macrophages. Similar to excessive intracellular cholesterol and phospholipids, oritavancin accumulation in macrophages resulted in deposition of concentric lamellar structures, finely granular material, or less-defined osmiophilic material³⁶. The appearance mimicked morphologic abnormalities noted in mixed-lipid storage disorders, invoking concern that these cellular alterations within macrophages reduced phagocytic function, potentially increasing risk for infection particularly due to fungi and mycobacteria. A study by Baquir et al. (2012) addressed these concerns by measuring killing function by 2 lines of macrophages against *S. aureus*, *Candida albicans*, and *Acinetobacter baumannii* when exposed to therapeutic dosing of oritavancin³⁷. The investigators found that both lines of macrophages still killed pathogens after exposure to oritavancin but with the following differences in effect: *S. aureus* killing was enhanced by oritavancin, *C. albicans* killing was unchanged, and *A. baumannii* killing was unchanged among one line of macrophages and moderately reduced among the other line. Based on these results, the investigators concluded that oritavancin accumulation within macrophages does not significantly alter macrophage killing of key pathogens such as *S. aureus*.

In August of 2014 after completion of SOLO I and SOLOII, the FDA approved oritavancin for the treatment of ABSSSI due to gram-positive organisms in adults 18 years of age.

7.0 Conclusion

Oritavancin is a safe and effective drug for the treatment ABSSSI. It also has demonstrated bactericidal activity against multidrug resistant gram-positive bacteria such as VRE, MRSA, VISA, hVISA, and VRSA. The one-time intravenous dosing is an appealing solution to the economic burden that hospitalization and outpatient IV therapy for ABSSSI exerts upon the healthcare system. However, further assessment of cost and providers' willingness to prescribe oritavancin over other antibiotics currently available is needed.

8.0 Expert opinion

Oritavancin offers advantages over current IV antibiotic therapy for the treatment of ABSSSI caused by *Staphylococci* and *Streptococci*. Its prolonged half-life allows treatment with a single infusion and does not require therapeutic drug monitoring. In comparison to current antibiotics approved for the treatment of ABSSSI, it is the only agent with a one-time dosing regimen. This dosing strategy is attractive, potentially avoiding hospitalization for IV antibiotics and the need for home health or skilled nursing facility care for outpatient IV antibiotic administration. One-time IV dosing may also improve therapeutic compliance compared to oral step-down therapy. Dalbavancin is in the beginning of a Phase 4 trial comparing one time versus the current two time dosing strategy for the treatment of ABSSSI. If the one time dosing strategy of dalbavancin is successful, the drug will compete strongly against oritavancin.

In addition to treatment of ABSSSI, oritavancin holds promise in treating other infectious diseases such as bacteremia, endocarditis, and *C. difficile* colitis based upon efficacy in a Phase II clinical trial in treatment of *S. aureus* bacteremia and animal models of infective endocarditis^{23, 32}. In a rabbit model of MRSA endocarditis, oritavancin is as effective as vancomycin in clearance of bacteremia and reduction in bacterial counts in vegetations and tissues³⁸. In a rat model of MSSA endocarditis, oritavancin, vancomycin, oxacillin, and daptomycin therapy significantly decreased *S. aureus* densities in vegetations by bioluminescent assay³⁹. Oritavancin has also performed well in animal models of endocarditis due to *E. faecalis*, maintaining activity against vancomycin-susceptible and *vanA* and *vanB* phenotypes⁴⁰. Similarly, oritavancin in combination with gentamicin proved synergistic against all three strains of *E. faecalis* in the treatment of left-sided endocarditis without the emergence of mutants resistant to either component of therapy⁴¹. Further studies are needed to study oritavancin's effectiveness in the treatment of *E. faecalis* and *E. faecium* infection in humans.

Drug-resistant *S. aureus* infections will continue to pose significant treatment challenges in the years to come⁴². Current data on efficacy in animal models and initial clinical trials should inspire further study of oritavancin in treatment of conditions that require prolonged IV therapy such as bacteremia, endocarditis, and meningitis. Further investigation into osteomyelitis and septic arthritis as potential future therapeutic targets for oritavancin is also warranted.

Whether or not physicians would be willing to prescribe oritavancin depends on whether one-time infusion will prevent hospitalization for ABSSSI and complications from

prolonged IV therapy such as catheter-associated bloodstream infections, venous thrombosis, and thrombophlebitis. Ideally, patients could receive their first dose of oritavancin in the outpatient setting such as an emergency department or outpatient clinic without necessitating hospital admission, PICC line placement, and arrangements for home infusion services. Conversely, patients with more complicated ABSSSI that require admission for sepsis or surgical drainage could benefit from oritavancin's dosing strategy with shorter hospital stays and potentially no need for home infusion services or oral step-down therapy.

In addition, further data are needed to determine whether oritavancin's one time IV dosing strategy is cost effective. Costs of antibiotics for ABSSSI vary significantly (Table 2). However, the costs do not take into account costs of home IV infusion services nor can they account for potential non-compliance with oral therapy, relapse of infection, and hospital readmission. In 5 years' time, if use of oritavancin is proven to be cost-effective in shortening duration or preventing hospitalization and preventing complications of IV therapy, it will be sought as an effective alternative to current antibiotics for the treatment of ABSSSI.

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Abbreviations and units

ABSSSI	Acute bacterial skin and skin structure infection
ALT	Alanine aminotransferase
AUC	Area under concentration-time curve
CFU	Colony-forming units
CoNS	Coagulase negative <i>Staphylococci</i>
g	Gram
T_{1/2}	Half-life
hVISA	Heterogeneous vancomycin-intermediate <i>Staphylococcus aureus</i>
IV	Intravenous
L	Liters

MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
µg/mL	Microgram per milliliter
mg/kg	Milligram per kilogram
mg/L	Milligram per liter
MIC	Minimum inhibitory concentration
PD	Pharmacodynamic
SD	Standard deviation
ULN	Upper limit of normal
TEAE	Treatment-emergent adverse event
T>MIC	Time above MIC
VISA	Vancomycin-intermediate <i>Staphylococcus aureus</i>
VRSA	Vancomycin-resistant <i>Staphylococcus aureus</i>
VRE	Vancomycin-resistant <i>Enterococcus</i>

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Drug summary box

Drug Name	Oritavancin	
Phase	Completed Phase III trials	
Indication	Acute bacterial skin and skin structure infections	
Pharmacology description/ mechanism of action	Semi-synthetic lipoglycolipopeptide, bactericidal, disrupts cell membrane and inhibits the transglycosylation and transpeptidation steps of cell wall synthesis in a dose-dependent manner	
Route of administration	Intravenous	
Chemical Structure
Pivotal Trial(s)	SIMPLIFI ³¹ SOLO I ²⁹ SOLO II ²⁸	

Table 1

Oritavancin's spectrum of activity

Organism	Oritavancin MIC ₅₀ /MIC ₉₀ (µg/mL)
Methicillin-resistant <i>Staphylococcus aureus</i> ^{43, #}	0.06/0.06
Methicillin-sensitive <i>Staphylococcus aureus</i> ^{43, #}	0.03/0.06
Coagulase negative <i>Staphylococci</i> ^{43, #}	0.015/0.06
<i>Streptococcus anginosus</i> group ^{43, #}	0.008/0.015
<i>Streptococcus pyogenes</i> ^{43, #}	0.03/0.12
<i>Streptococcus agalactiae</i> ^{43, #}	0.03/0.12
<i>Enterococcus faecalis</i> ^{43, #}	0.015/0.06
<i>Enterococcus faecium</i> , Vancomycin-Susceptible ^{43, #}	0.008/ 0.008
<i>Enterococcus faecium</i> , Vancomycin-Resistant ^{43, #}	0.06/0.12
<i>Listeria monocytogenes</i> ²¹	0.008/0.015
<i>Corynebacterium</i> species ²¹	0.008/0.06
<i>Micrococcus</i> species ²¹	0.008/ 0.008

for United States isolates

Table 2Prices of Commonly Used Anti-Staphylococcal Drugs for ABSSSI¹

Antibiotic	Price per dose	Price per Treatment Course
Ceftaroline	\$151.62 ^a	\$2122.68 ^b
Dalbavancin	\$1788 ^c	\$5364 ^d
Daptomycin	\$455.04 ^c	\$3185.28 ^e
Linezolid	N/A	\$3644.29 ^f
Oritavancin	\$1160 ^g	\$3480 ^h
Tedizolid	N/A	\$2124.00 ⁱ
Telavancin	\$389.93 ^j	\$2729.51 ^e
Vancomycin	\$7.46 ^k	\$104.44 ^b

¹. Average wholesale price in U.S. Data obtained from Lexicomp Online®, UpToDate®, Hudson, Ohio: Lexi-Comp, Inc.; February 20, 2015.

^a. Same price for 400mg and 600mg reconstituted solution

^b. 7 day treatment course (twice daily)

^c. 500mg reconstituted solution

^d. One time dosing 1000mg followed by 500mg one week later

^e. 7 day treatment course (once daily)

^f. 10 day treatment course (twenty 600mg oral tablets)

^g. 400mg reconstituted solution

^h. 1200mg dose once

ⁱ. 6 day treatment course (six 200mg oral tablets)

^j. 750mg reconstituted solution

^k. 1000mg reconstituted solution