intravenously every 12 hours. At lefamulin MIC_{90} values for *S. aureus* and *S. pneumoniae,* the cumulative probability of target attainment over the MIC distribution used was ≥ 99.9%.

Comparison of lefamulin 100 mg and 150 mg administered intravenously every 12 hours to patients with skin and skin structure infection in a phase II clinical trial showed similar rates of resolution in the area of erythema.

5d. Excretion

Lefamulin is predominately excreted in feces (Wicha *et al.,* 2010b). After administration of carbon 14 (^{14}C)–labeled lefamulin to rats, 80% was recovered from the feces. A further 13% appeared in the urine. The plasma half-life in patients with skin and skin structure infection was 11.0–13.2 l/h. Linear lefamulin clearance was demonstrated in a single dose-escalation study of lefamulin 25 mg to 400 mg clearance with clearance of 18–25 l/h.

5e. Drug interactions

Lefamulin is metabolized by CYP450 enzymes. *In vitro* lefamulin was shown to act as both a substrate and an inhibitor for CYP3A (Schmidt *et al.,* 2011). Induction experiments using human hepatocytes did not reveal any induction of CYP1A2 or CYP3A4 by lefamulin. Human pharmacokinetic studies of lefamulin co-administered with ketoconazole showed only a mild effect on lefamulin pharmacokinetics. Co-administration of lefamulin and midazolam demonstrated no effect on midazolam pharmacokinetics. Currently, no dose adjustment is recommended when administering lefamulin with either CYP3A4 substrates or inhibitors.

6. ADVERSE REACTIONS AND TOXICITY

In phase I and II clinical trials, lefamulin has been generally well tolerated. Headache (8%) and nausea (7%) are the most commonly reported side effects (Table 89.3). Infusion site reactions and pain were commonly reported (5–10%) after administration of both lefamulin and placebo. Isolated increases in alanine aminotransferase and aspartate aminotransferase levels were comparable between lefamulin and vancomycin. No serious adverse events or hypersensitivity reactions have been reported.

7. CLINICAL USES OF THE DRUG

Lefamulin is currently not licensed for clinical use. In a phase II study in patients with ABSSSIs, lefamulin was shown to be comparable to vancomycin (Prince *et al.,* 2013). A phase III randomized, double-blind, double-dummy study to compare the efficacy and safety of lefamulin versus moxifloxacin

Table 89.3. Summary of toxicity data for adult patients treated with lefamulin.

		Comparator (% of patients)	
Adverse event	**Lefamulin[a,b] (% of patients)**	**Placebo[a]**	**Vancomycin[b]**
Creatine phosphokinase increased	1.7%		
Dermatitis	1.1%		
Gastrointestinal			
Abdominal pain	1.7%		
Alanine aminotransferase increased	2.2%		4.5%
Aspartate aminotransferase increased	1.1%		3.0%
Constipation	0.6%		4.5%
Diarrhea	3.9%		6.1%
Nausea	6.7%		15.2%
Vomiting	2.8%		4.5%
Headache	7.8%		15.2%
Infusion site			
Infusion site pain	4.5%	7.7%	
Infusion site phlebitis	3.4%	5.1%	
Infusion site reaction	1.7%	10.3%	
Insomnia	0.0%		3.0%
Phlebitis	1.1%		
Pruritus	2.8%		12.1%
Sacral pain	0.6%	2.6%	
Tinnitus	1.1%		
Transient hypertension	0.6%		
Vulvovaginal mycotic infection	1.1%		

[a]Based on data from 38 lefamulin-treated patients and 39 placebo-treated patients.
[b]Based on data from 141 lefamulin-treated patients and 66 vancomycin-treated patients.
Sources: Compiled from the following references: Prince *et al.,* 2013; Wicha *et al.,* 2010a.