These features are considered to contribute to dalbavancin's antimicrobial activity.

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

Currently, dalbavancin is available only in the i.v. form, owing to the poor systemic absorption displayed by it and other glycopeptide antibiotics.

4a. Adults

The initial FDA-approved dosage consisted of dalbavancin, 1000 mg on the first day, followed by 500 mg 7 days later, which was well tolerated and associated with a higher clinical response rate than the comparator regimens (Dorr *et al.*, 2005; Durata, 2015). This regimen is also approved in Europe by the European Medicines Agency. Recently, the FDA approved a single 1500-mg infusion of dalbavancin based on a phase III study, which demonstrated that the single dose was noninferior to the two-dose regimen and has a similar safety profile. This single-dose regimen potentially removes logistical constraints related to delivery of the second dose, enhancing its ease of use (Dunne *et al.*, 2016a; Dunne *et al.*, 2016b).

4b. Newborn infants and children

To date, there has been a single dalbavancin phase I study in children (Bradley *et al.*, 2015). Dalbavancin is currently not approved in the USA or Europe for those ≤ 18 years of age.

4c. Pregnant and lactating mothers

Dalbavancin is an FDA pregnancy category C drug. It should be used in pregnancy only if the benefit justifies the potential risk to the fetus. In pregnant rats and rabbits, there were no treatment-related malformations or embryo-fetal toxicity at clinically relevant dalbavancin exposures. It is unknown whether dalbavancin or its metabolite is excreted in human milk (Durata, 2015).

4d. Those requiring altered dosages

PATIENTS WITH IMPAIRED RENAL FUNCTION

A mean renal clearance of 0.042 l/h suggests that dalbavancin may not require a dose adjustment for patients with mild-to-moderate renal impairment (Marbury *et al.*, 2009). Pharmacokinetic parameters (i.e. maximum concentration [C_{max}]; area-under-the-concentration-time curve [AUC]) studied over a 7-day period were found to be similar among subjects with mild renal impairment, defined as creatinine clearance (CL_{Cr}) of 50–80 ml/min (C_{max}: 266.8 ± 42.3 mg/l; AUC_{0-7}: 9714 ± 1406 mg/lh) and those with normal renal function (C_{max}: 248.8 ± 33 mg/l; AUC_{0-7}: 8992 ± 1362 mg/lh) after receiving a 1000-mg dose (Marbury *et al.*, 2009). Patients with moderate renal impairment (CL_{Cr}: 30–49 ml/min) receiving 1000 mg also showed similar pharmacokinetics to those with normal renal function, although the mean $AUC_{0\text{-}inf}$ was approximately 50% higher compared with normal patients (Marbury *et al.*, 2009). In patients with severe renal impairment (CL_{Cr} < 30 ml/min), the C_{max} increased nearly 30% after the first week and AUC_{0-7} increased by approximately 17%. It appears that dose adjustments may be necessary for patients with CL_{Cr} < 30 ml/min, as reflected in the current recommendations (750 mg followed 1 week later by 375 mg). For those with end-stage renal disease requiring dialysis support, concentrations from a 500-mg dose were similar to those without any renal impairment. A smaller dose of 500 mg may suffice for dialysis patients, considering that hemodialysis was not an important route of elimination for dalbavancin (Marbury *et al.*, 2009).

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Currently, no dalbavancin dose adjustments are recommended for patients with mild, moderate, or severe hepatic impairment (Marbury *et al.*, 2009). Pharmacokinetic parameters were similar to subjects with normal hepatic function on a 1000-mg dose followed by 500 mg 7 days later (Marbury *et al.*, 2009). A slightly lower AUC and higher clearance were seen in subjects with moderate and severe hepatic impairment but were likely due to volume changes from ascites and edema.

OLDER ADULTS

A population pharmacokinetic study, which utilized data from phase II and III clinical trials, determined that age, gender, race, and serum albumin were not influential factors for pharmacokinetic parameters, suggesting no dosage adjustments will be required based on these variables (Buckwalter and Dowell, 2005). In a recent analysis of 1778 patients treated with dalbavancin, 313 patients (17.7%) were 65 years of age or older. The efficacy and tolerability of dalbavancin were similar to comparator regardless of age (Durata, 2015; Dunne *et al.*, 2016b).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

Dalbavancin is not available orally. Total protein binding of dalbavancin is concentration independent, reversible, and estimated to be 93%. Yet the small free fraction left over is capable of bactericidal activity (Cavaleri *et al.*, 2002; Bowker *et al.*, 2006; Cavaleri *et al.*, 2005). The plasma concentration-time profile of dalbavancin initially has a steep decline during the 24- to 48-hour distribution phase, which slopes down into a slower terminal elimination phase, extending out to 600–800 hours (Cavaleri *et al.*, 2005; Dorr *et al.*, 2005).

5b. Drug distribution

Dalbavancin exhibits linear, dose-proportional pharmacokinetics with a $t_{1/2}$ of approximately 7 days (Leighton *et al.*,