37°C. The reliability of high-performance liquid chromatography measurements of daptomycin mixed into icodextrin solutions was unacceptable, and therefore stability in icodextrin cannot be studied (Peyro Saint Paul *et al.*, 2011).

4a. Adults

The approved dosage regimen after clinical trials for complicated skin and skin structure infections (cSSSIs) is 4 mg/kg once daily. For bacteremia and endocarditis, a dosing regimen of 6 mg/kg once daily is recommended. Administration is by i.v. infusion in 0.9% sodium chloride injection over a 30-minute period. Owing to the risk of side effects, daptomycin should not be dosed more frequently than once daily. Instead of a 30-minute infusion, two studies evaluated the use of bolus injections. A bolus injection over 10 seconds of the 6 mg/kg dose resulted in comparable exposures of 700 mgh/l for the bolus group (N = 16) and 690 mgh/l for the 30-minute infusion group (Aoki *et al.*, 2015). Bolus injections of 2 minutes also resulted in similar exposures compared with the standard 30-minute infusions (Chakraborty *et al.*, 2009). In both studies, which used limited numbers of patients, no differences in adverse events have been shown. Daptomycin cannot be administered i.m.

However, the on-label dosages of 4 and 6 mg/kg/day are now considered too low by some authors. As has been reviewed recently by Senneville *et al.* (2016), higher dosages of daptomycin (i.e. ≥ 10 mg/kg/day) might be needed to prevent the risk of selecting resistance and to treat endocarditis and bacteremia, including those cases associated with intravascular catheter and implant-related infections.

For the average population, daptomycin is mostly dosed based on actual body weight. To compare the effect when dosages were based on ideal body weight, two groups were compared. One group was dosed based on actual body weight (N = 69 patients) and the other on ideal body weight (N = 48 patients). There was no statistically significant difference in clinical success between the groups (88.9% for actual body weight compared with 89.1% for ideal body weight; $p = 0.97$). After adjustment for gender, age, body mass index, concomitant 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, infection type, and organism type, clinical success rates remained similar between groups (adjusted OR: 0.68 in favor of actual body weight; 95% CI: 0.13–3.55). Microbiological outcomes, length of stay, mortality, and adverse effects were also similar between groups (Ng *et al.*, 2014).

4b. Newborn infants and children

No dosing regimen adaptations have been recommended for children, and the optimal dosing regimen still needs to be determined (Garazzino *et al.*, 2016). The pharmacodynamics, safety, and effectiveness of daptomycin in infants and children are not well established (Ardura *et al.*, 2007). Some data suggest that rates of adverse events in children are similar to those in adults (Garazzino *et al.*, 2016; Syriopoulou *et al.*, 2016). However, drug exposure after a single weight-adjusted daptomycin dose is reduced in younger children compared with adolescents (Abdel-Rahman *et al.*, 2008; Bradley *et al.*, 2014). This is due to an apparent age-associated change in total plasma clearance (see section 5d, Excretion). Further data are needed to adjust the dosing regimen according to the increased renal clearance of daptomycin in severe infections in children. Clinical experience reports on the outcome of daptomycin treatment in children are scarce. No data are currently available for daptomycin use in neonates. The excretion of daptomycin in children is discussed later under section 5d, Excretion.

4c. Pregnant and lactating mothers

There are no clinical data on the use on daptomycin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal or fetal development, parturition, or postnatal development (Summary of Product Characteristics, 2016).

Clinical data on the excretion of daptomycin in breast milk are scarce. In a single human case study, a breastfeeding mother was treated with daptomycin for an infection caused by MRSA (Buitrago *et al.*, 2009). She received daptomycin i.v. daily for 28 days at a dose of 500 mg/day (6.7 mg/kg/day), and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 mg/l, which is low. The estimated milk/plasma ratio was 0.0012. This low concentration supports the idea that daptomycin, given its high protein binding of 90–93% and a high molecular weight of 1620.67 daltons, will be excreted minimally into breast milk (Mitrano *et al.*, 2009).

4d. Those requiring altered dosages

Several well-known patient groups for whom dosages might be changed are discussed, but there may be other special situations for which altered dosages may be needed. An example is the different pharmacokinetics during cardiac surgery, as is shown by Nguyen *et al.* (2011) for patients during cardiopulmonary bypass surgery. In this group of patients, therapeutic drug monitoring might be needed.

PATIENTS WITH IMPAIRED RENAL FUNCTION

The recommendation of the authorities for dosing of daptomycin, as described in the Summary of Product Characteristics (2016), is based on the indication as well as the creatinine clearance. Routine once-daily doses of daptomycin are used for adults with creatinine clearance ≥ 30 ml/min (Package Insert, 2007; Summary of Product Characteristics, 2016). However, because renal excretion is the primary route of elimination, dose adjustment is required in patients with severe renal insufficiency (creatinine clearance rate < 30 ml/min), including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (see section 5d, Excretion)