Daptomycin *(BAN, USAN, rINN)*

Daptomicina; Daptomycine; Daptomycinum; LY-146032. *N*-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine 1.13-3.4-lactone.

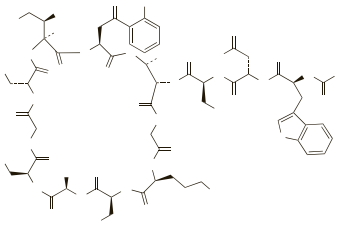
Даптомицин

$C_{72}H_{101}N_{17}O_{26}$ = 1620.7.

CAS — 103060-53-3.

ATC — J01XX09.

ATC Vet — QJ01XX09.



Adverse Effects and Precautions

The most common adverse effects associated with daptomycin are gastrointestinal effects including nausea and vomiting, constipation, diarrhoea, and dyspepsia. Headache, insomnia, dizziness, and fever may occur. Injection site reactions have occurred. Effects on the skin have included rash and pruritus. Abnormal liver function tests and jaundice have been reported. Other reported adverse effects include hypertension or hypotension, renal failure, dyspnoea, and anaemia. There have been rare cases of hypersensitivity, anaphylaxis, and infusion reactions.

Elevated plasma creatine phosphokinase (CPK) concentrations during daptomycin therapy may be associated with muscle pain and/or weakness, myositis, myopathy, and rarely rhabdomyolysis; patients with renal impairment or taking other drugs known to cause myopathy (see Interactions, below) may be at increased risk. All patients should be monitored for the development of muscle pain or weakness, and plasma CPK concentrations measured once weekly. More frequent measurements should be performed in those with an increased risk of myopathy, or with a baseline CPK concentration greater than 5 times the upper limit of normal (ULN), or who develop signs of myopathy. Daptomycin should be stopped in patients with signs of myopathy and CPK concentrations greater than 5 times the ULN, or in those without reported signs of myopathy but with CPK concentrations greater than 10 times the ULN.

Daptomycin should be given with caution and in reduced dosage to patients with renal impairment; clinical response and renal function should be monitored closely.

Consideration should be given to stopping daptomycin therapy in patients who develop signs or symptoms of peripheral neuropathy.

Effects on the lungs. Bronchiolitis obliterans organising pneumonia with eosinophilic infiltration has been reported in an 84-year-old man after 4 weeks of daptomycin therapy;[1] clinical improvement occurred after the drug was stopped. The mechanism of toxicity was unknown and the authors suggested that it might be associated with epithelial injury caused by daptomycin accumulating in the alveolar spaces.

A 60-year-old man receiving daptomycin developed eosinophilic pneumonia resulting in respiratory failure that required mechanical ventilation;[2] he improved after stopping the drug and starting corticosteroid therapy.

1. Cobb E, *et al.* Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother* 2007; **41:** 696–701.
2. Hayes D, *et al.* Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007; **54:** e211–e213.

Pregnancy. Intravenous daptomycin, 4 mg/kg daily for 14 days, was successfully used to treat pyelonephritis associated with vancomycin-resistant enterococci (VRE) in a 27-week pregnant woman; no neonatal abnormalities were reported.[1]

1. Shea K, *et al.* Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. *Ann Pharmacother* 2008; **42:** 722–5.

Interactions

There may be an increased risk of myopathy if daptomycin is given with other drugs also known to have this adverse effect, such as statins, fibrates, and ciclosporin. Licensed product information recommends stopping the latter if possible; otherwise, plasma creatine phosphokinase concentrations should be measured more than once weekly in addition to the usual precautions (see Adverse Effects and Precautions, above).

Daptomycin is mainly excreted by renal filtration and caution is advised if given with drugs that reduce renal filtration, such as NSAIDs and selective inhibitors of cyclo-oxygenase-2, since plasma concentrations of daptomycin may be increased.

Daptomycin has been reported to interact with a particular reagent used in some assays of PT-INR resulting in apparent prolongation of PT and elevation of INR.

Antimicrobial Action

Daptomycin is a lipopeptide antibacterial that is reported to have a spectrum of antibacterial activity similar to that of vancomycin (p.359) and greater potency against most Gram-positive bacterial strains *in vitro*; it is inactive against Gram-negative bacteria. Daptomycin disrupts the bacterial cell membrane potential by binding to the cell membranes in a calcium-dependent process, but without entering the cytoplasm, thus inhibiting the synthesis of protein, DNA, and RNA.

Daptomycin has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci.

It is reported to show antimicrobial synergy *in vitro* with aminoglycosides, beta lactams, and rifampicin against *Staph. aureus* (including meticillin-resistant strains) and enterococci (including vancomycin-resistant strains).

Resistance to daptomycin has been shown in clinical studies but only rarely; the mechanism of resistance has not been identified.

◊ Reviews.

1. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. *Clin Infect Dis* 2007; **45:** 601–8.

Pharmacokinetics

Daptomycin is not absorbed to any significant extent after oral doses. The pharmacokinetics of daptomycin are generally linear at intravenous doses ranging from 4 to 12 mg/kg once daily. Peak plasma concentrations are achieved within 0.5 to 0.8 hours. It is distributed mainly into the extracellular space with a volume of distribution of about 0.1 litres/kg. Daptomycin crosses the blood-brain barrier and the placenta. It is about 90% bound to plasma proteins, mainly serum albumin.

In-vitro studies indicate that daptomycin is not metabolised by, and does not affect, the cytochrome P450 isoenzyme system. Little or no metabolism is thought to take place although 4 minor metabolites have been detected in the urine.

Daptomycin is excreted mainly via renal filtration with about 78% and 6% of a dose recovered in the urine and faeces, respectively. It has an elimination half-life of about 8 hours after an intravenous dose of 4 mg/kg once daily for 7 days and is prolonged in patients with renal impairment; a two- to threefold increase has been reported in those with severe impairment or end-stage renal disease.

Daptomycin is removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Dvorchik B, *et al.* Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2004; **48:** 2799–2807.

Uses and Administration

Daptomycin is given by intravenous infusion over 30 minutes for the treatment of complicated Gram-positive infections of the skin and soft tissues, and *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, caused by meticillin-susceptible and meticillin-resistant strains.

For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

For the treatment of skin and soft-tissue infections, daptomycin is given in a dose of 4 mg/kg once daily for 7 to 14 days. A higher dose of 6 mg/kg once daily is given for 2 to 6 weeks in the treatment of bacteraemia.

For details of dosage modification in patients with renal impairment, see below.

Daptomycin has also been investigated for the treatment of vancomycin-resistant enterococcal infections, complicated urinary-tract infections, and community-acquired pneumonia.

◊ References.

1. Fenton C, *et al.* Daptomycin. *Drugs* 2004; **64:** 445–55.
2. Steenbergen JN, *et al.* Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; **55:** 283–8.
3. Schriever CA, *et al.* Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am J Health-Syst Pharm* 2005; **62:** 1145–58.
4. French GL. Bactericidal agents in the treatment of MRSA infections—the potential role of daptomycin. *J Antimicrob Chemother* 2006; **58:** 1107–17.
5. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 2007; **67:** 1483–1512.
6. Enoch DA, *et al.* Daptomycin. *J Infect* 2007; **55:** 205–13.
7. Weis F, *et al.* Daptomycin, a lipopeptide antibiotic in clinical practice. *Curr Opin Investig Drugs* 2008; **9:** 879–84.
8. Forrest GN, *et al.* Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother* 2008; **42:** 213–17.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, including those receiving dialysis, the intravenous dosage of daptomycin should be modified to 4 mg/kg once every 48 hours in the treatment of skin and soft-tissue infections, and to 6 mg/kg once every 48 hours in the treatment of bacteraemia.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Cubicin; ***Gr.:*** Cubicin; ***Israel:*** Cubicin; ***Port.:*** Cubicin; ***UK:*** Cubicin; ***USA:*** Cubicin.

Demeclocycline *(BAN, rINN)*

Demeclociclina; Déméclocycline; Demeclocyclinum; Demeklocyklin; Demeklosykliini; Demethylchlortetracycline. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyltetracycline.

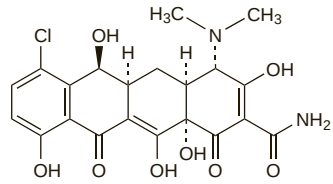
Демеклоциклин

$C_{21}H_{21}ClN_2O_8$ = 464.9.

CAS — 127-33-3 (demeclocycline); 13215-10-6 (demeclocycline sesquihydrate).

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.



Pharmacopoeias. In *US.*

USP 31 (Demeclocycline). A yellow, odourless crystalline powder. Sparingly soluble in water; soluble 1 in 200 of alcohol and 1 in 40 of methyl alcohol; dissolves readily in 3N hydrochloric acid and in alkaline solutions. pH of a 1% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Demeclocycline Hydrochloride *(BANM, rINNM)*

Déméclocycline, chlorhydrate de; Demeclocyclini hydrochloridum; Demeklociklin-hidroklorid; Demeklociklino hidrochloridas; Demeklocyklin-hydrochlorid; Demeklocyklinhydroklorid; Demeklocykliny chlorowodorek; Demeklosiklin Hidroklorür; Demeklosykliinihydrokloridi; Demethylchlortetracycline Hydrochloride; Hidrocloruro de demeclociclina.

Демеклоциклина Гидрохлорид

$C_{21}H_{21}ClN_2O_8$,HCl = 501.3.

CAS — 64-73-3.

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Demeclocycline Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Soluble or sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

USP 31 (Demeclocycline Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 60 of water and 1 in 50 of methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone and in chloroform; sparingly soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Phototoxic reactions occur more frequently with demeclocycline than with other tetracyclines and patients should avoid direct exposure to sunlight or artificial ultraviolet light.

Reversible nephrogenic diabetes insipidus with polyuria, polydipsia, and weakness may occur in patients treated with demeclocycline, particularly with prolonged treatment and/or high doses. Plasma creatinine should be monitored in patients receiving demeclocycline for long periods for the treatment of inappropriate secretion of antidiuretic hormone, since tetracycline-induced renal impairment may not otherwise be apparent in the absence of oliguria. For a comment that the usefulness of demeclocycline for this indication may be limited by nephrotoxicity in patients with cardiac or hepatic disease, see Syndrome of Inappropriate ADH Secretion under Uses and Administration, below.