sue necrosis and can be given by intramuscular injection. Other hypersensitivity reactions have included rigors, angioedema, and, rarely, severe skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Other reported reactions include gastrointestinal disturbances, dizziness, headache, thrombocytopenia (especially at high doses), leucopenia, neutropenia, eosinophilia, disturbances in liver enzyme values, and pain, erythema, and thrombophlebitis or abscess at the injection site. Rare cases of agranulocytosis have occurred. Renal impairment and ototoxicity have been reported but both appear to be less frequent than with vancomycin.

Renal and auditory function should be monitored during prolonged therapy in patients with pre-existing renal impairment, and in those receiving other ototoxic or nephrotoxic drugs, although opinions conflict as to whether increased risk of nephrotoxicity exists with combined therapy with drugs such as the aminoglycosides. In general, periodic blood counts and liver- and renal-function tests are advised during treatment.

No relationship has yet been established between plasma concentration and toxicity, and plasma-concentration monitoring is not generally considered necessary. Dosage adjustment is required in renal impairment.

Hypersensitivity. Although there have been occasional reports of cross-sensitivity to teicoplanin in patients hypersensitive to vancomycin,[1-4] the majority of reports suggest that cross-sensitivity is very rare and teicoplanin can usually be used in patients intolerant of vancomycin.[5-7]

1. McElrath MJ, *et al.* Allergic cross-reactivity of teicoplanin and vancomycin. *Lancet* 1986; **i:** 47.
2. Grek V, *et al.* Allergic cross-reaction of teicoplanin and vancomycin. *J Antimicrob Chemother* 1991; **28:** 476–7.
3. Marshall C, *et al.* Glycopeptide-induced vasculitis—cross-reactivity between vancomycin and teicoplanin. *J Infect* 1998; **37:** 82–3.
4. Kwon HS, *et al.* A case of hypersensitivity syndrome to both vancomycin and teicoplanin. *J Korean Med Sci* 2006; **21:** 1108–10.
5. Schlemmer B, *et al.* Teicoplanin for patients allergic to vancomycin. *N Engl J Med* 1988; **318:** 1127–8.
6. Smith SR, *et al.* Teicoplanin administration in patients experiencing reactions to vancomycin. *J Antimicrob Chemother* 1989; **23:** 810–12.
7. Wood G, Whitby M. Teicoplanin in patients who are allergic to vancomycin. *Med J Aust* 1989; **150:** 668.

Red-man syndrome. Although teicoplanin is believed[1,2] to be less likely than vancomycin to induce the red-man syndrome, symptoms consistent with the syndrome have nevertheless been reported after intravenous use.[3]

1. Sahai J, *et al.* Comparison of vancomycin- and teicoplanin-induced histamine release and "red man syndrome". *Antimicrob Agents Chemother* 1990; **34:** 765–9.
2. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
3. Dubettier S, *et al.* Red man syndrome with teicoplanin. *Rev Infect Dis* 1991; **13:** 770.

Antimicrobial Action

As for Vancomycin Hydrochloride, p.359, although in general teicoplanin is more active against susceptible strains. In particular, it may be more active *in vitro* against enterococci and some anaerobic organisms, including strains of *Clostridium*. However, some coagulase-negative staphylococci are less sensitive to teicoplanin than to vancomycin.

Acquired resistance to teicoplanin has developed in staphylococci during treatment with teicoplanin. Cross-resistance with vancomycin has occurred in staphylococci and enterococci.

Pharmacokinetics

Teicoplanin is poorly absorbed from the gastrointestinal tract. After a 400-mg intravenous dose, peak plasma concentrations 1 hour later are reported to be in the range 20 to 50 micrograms/mL. It is well absorbed on intramuscular injection with a bioavailability of about 90%; after a dose of 3 mg/kg intramuscularly, peak plasma concentrations of 5 to 7 micrograms/mL have been reported after 2 to 4 hours.

The pharmacokinetics of teicoplanin are triphasic, with a biphasic distribution and a prolonged elimination. Penetration into the CSF is poor. It is taken up into white blood cells, and about 90 to 95% of teicoplanin in plasma is protein bound. It is excreted almost entirely by glomerular filtration in the urine, as unchanged drug. The terminal half-life is prolonged, but reported half-lives have ranged from about 30 to 190 hours or longer, depending on the sampling time; an effective clinical half-life of about 60 hours has been suggested for use in calculating dosage regimens. Half-life is increased progressively with increasing degrees of renal impairment. Teicoplanin is not removed by haemodialysis.

Teicoplanin is a mixture of several components, the pharmacokinetics of which have been shown to vary slightly, depending on their lipophilicity.

◊ Reviews.

1. Wilson APR. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet* 2000; **39:** 167–83.

Uses and Administration

Teicoplanin is a glycopeptide antibiotic that may be used as an alternative to vancomycin (p.360) in the treatment of serious Gram-positive infections where other drugs cannot be used, including the treatment and prophylaxis of infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis, and suspected infection in neutropenic or otherwise immunocompromised patients. Teicoplanin, given orally, has been suggested as a possible alternative to vancomycin or metronidazole in antibiotic-associated colitis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Teicoplanin is given intravenously, as a bolus dose or by infusion over 30 minutes, or by intramuscular injection. The usual mean dose is 6 mg/kg intravenously or intramuscularly initially, followed by 3 mg/kg intravenously or intramuscularly on each subsequent day of treatment (in practice this equates to a usual dose of 400 mg initially followed by 200 mg daily, except in patients weighing more than 85 kg in whom it is adapted accordingly). In more severe infections, 6 mg/kg may be given every 12 hours for the first 3 doses, followed by 6 mg/kg daily.

For the prophylaxis of endocarditis in high-risk patients undergoing dental or other procedures who are unable to receive penicillin, teicoplanin may be given in a single dose of 400 mg by intravenous injection, with gentamicin, before the procedure. A similar dose of teicoplanin is given for prophylaxis in orthopaedic surgery at induction of anaesthesia.

In children, a loading dose of 10 mg/kg every 12 hours for 3 doses is followed by 6 to 10 mg/kg daily, depending on the severity of infection. In neonates, a loading dose of 16 mg/kg on the first day is followed by maintenance doses of 8 mg/kg daily, given by intravenous infusion. Although no relationship between plasma concentrations and toxicity has been established, the *BNF* suggests that the former may sometimes be used as a guide to optimise treatment: trough concentrations should be above 10 micrograms/mL (15 to 20 micrograms/mL in patients with endocarditis) but less than 60 micrograms/mL.

Dosage should be adjusted in patients with impaired renal function (see Administration in Renal Impairment, below).

◊ Reviews.

1. Brogden RN, Peters DH. Teicoplanin: a reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 823–54.
2. Murphy S, Pinney RJ. Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J Clin Pharm Ther* 1995; **20:** 5–11.
3. de Lalla F, Tramarin A. A risk-benefit assessment of teicoplanin in the treatment of infections. *Drug Safety* 1995; **13:** 317–28.
4. Periti P, *et al.* Antimicrobial prophylaxis in orthopaedic surgery: the role of teicoplanin. *J Antimicrob Chemother* 1998; **41:** 329–40.
5. Schaison G, *et al.* Teicoplanin in the treatment of serious infection. *J Chemother* 2000; **12** (suppl 5): 26–33.

Administration in renal impairment. Doses of teicoplanin should be adjusted in patients with renal impairment, though reduction is not required until the fourth day of treatment. Teicoplanin should be given in usual doses for the first 3 days of therapy, thereafter the dose is adjusted according to creatinine clearance (CC):

- CC 40 to 60 mL/minute: half initial dose given daily or initial dose given every 2 days
- CC less than 40 mL/minute: one-third initial dose given daily or initial dose given every 3 days

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Targocid; Teicox; Teiklonal; Terbiox; ***Austral.:*** Targocid; ***Austria:*** Targocid; ***Belg.:*** Targocid; ***Braz.:*** Bactomax; Coplaxil†; Kirom; Targocid; Teicon; Teiconin†; Teicozid; ***Chile:*** Targocid; ***Cz.:*** Targocid; ***Denm.:*** Targocid; ***Fin.:*** Targocid; ***Fr.:*** Targocid; ***Ger.:*** Targocid; ***Gr.:*** Targocid; ***Hong Kong:*** Targocid; ***Hung.:*** Targocid; ***India:*** Targocid; Ticocin; ***Indon.:*** Targocid; ***Irl.:*** Targocid; ***Israel:*** Targocid; ***Ital.:*** Targosid; ***Jpn:*** Targocid; ***Malaysia:*** Targocid; ***Mex.:*** Targocid; Teripol; ***Neth.:*** Targocid; ***Norw.:*** Targocid; ***NZ:*** Targocid; ***Pol.:*** Targocid; ***Port.:*** Targosid; ***S.Afr.:*** Targocid; ***Singapore:*** Targocid; ***Spain:*** Targocid; ***Swed.:*** Targocid; ***Switz.:*** Targocid; ***Thai.:*** Targocid; ***Turk.:*** Targocid; ***UK:*** Targocid; ***Venez.:*** Targocid.

Multi-ingredient: ***Ger.:*** Targobone.

Telithromycin *(BAN, USAN, rINN)*

HMR-3647; RU-66647; Télithromycine; Telithromycinum; Telitromicina; Telitromisin. (3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyloctahydro-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-{4-[4-(3-pyridyl)imidazol-1-yl]butyl}-10-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-2*H*-oxacyclotetradecino[4,3-*d*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone.

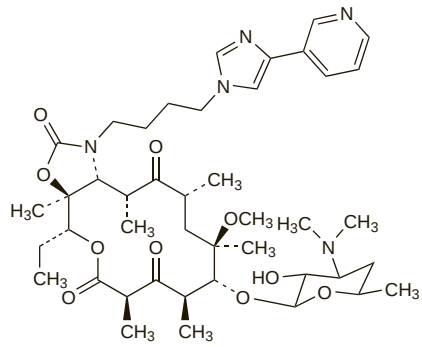
Телитромицин

$C_{43}H_{65}N_5O_{10}$ = 812.0.

CAS — 173838-31-8; 191114-48-4.

ATC — J01FA15.

ATC Vet — QJ01FA15.



Adverse Effects

Diarrhoea and other gastrointestinal disturbances such as nausea, vomiting, abdominal pain, and flatulence are among the most common adverse reactions after use of telithromycin. Severe, but usually reversible, hepatic dysfunction, including elevation of liver enzymes and hepatitis, with or without jaundice has been reported; however, there have been cases of fatal hepatotoxicity including fulminant hepatitis, hepatic necrosis, and hepatic failure. Effects on the CNS may include dizziness, headache, vertigo, and, occasionally, insomnia or drowsiness. Taste, and very rarely smell, disturbances may occur. Other less commonly reported adverse effects include paraesthesia, eosinophilia, skin rashes, and cardiovascular effects such as arrhythmias, hypotension, and bradycardia. Visual disturbances, particularly affecting accommodation, have occurred. Syncope, usually associated with the vagal syndrome, has been noted. Very rarely reported adverse effects include angioedema and anaphylaxis. There have been isolated cases of erythema multiforme, pseudomembranous colitis, and muscle cramps. Life-threatening acute respiratory failure has been reported in patients with myasthenia gravis (see also Precautions, below).

Effects on the eyes. Visual disturbances, namely blurred vision, difficulty with focusing, and diplopia have been associated with telithromycin. These have been reported to be more common in females under the age of 40 years and to occur in 1.1% of patients compared with 0.28% in those receiving a comparable antibacterial.[1] Licensed product information reports that symptoms are fully reversible, mostly mild to moderate in severity, and typically occur within a few hours of the first or second dose,

lasting for several hours and recurring upon subsequent dosing. They have not been associated with any ocular abnormality.

1. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in an 18-year-old man who received telithromycin for 5 days. Complete recovery of renal function occurred 2 weeks after starting symptomatic treatment with methylprednisolone.

1. Tintillier M, *et al.* Telithromycin-induced acute interstitial nephritis: a first case report. *Am J Kidney Dis* 2004; **44:** e25–e27.

Effects on the liver. Hepatotoxicity is an established adverse effect of telithromycin and may be severe. Of 3 case reports of serious liver toxicity in patients with no pre-existing hepatic impairment, after receiving telithromycin at the usual dose,[1] one patient spontaneously recovered, one required a liver transplant, and one died.

1. Clay KD, *et al.* Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann Intern Med* 2006; **144:** 415–20.

Effects on the skin. A 26-year-old woman with a history of rash to penicillin and sulfonamides developed toxic epidermal necrolysis after 13 doses of oral telithromycin for treatment of sinusitis; she was discharged 4 weeks after admission to hospital but had scars on her face and body and had lost her eyelashes.[1]

1. Health Canada. Telithromycin (Ketek): suspected association with toxic epidermal necrolysis. *Can Adverse React News* 2007; **17** (2): 2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 18/06/08)

Precautions

Telithromycin should not be given to patients with known hypersensitivity to it or to the macrolides; similarly, a history of hepatitis and/or jaundice associated with telithromycin or macrolides is a contra-indication.

Telithromycin is contra-indicated in patients with myasthenia gravis because it may exacerbate symptoms of the disease; exacerbations usually occur within 1 to 3 hours of the first dose. Fatalities have been reported.

Patients with a congenital or family history of QT interval prolongation should not receive telithromycin; it should be used with care in those with coronary heart disease, cardiac arrhythmias, and in those with hypokalaemia or hypomagnesaemia, due to its potential to prolong the QT interval. Certain medications may also increase the risk of cardiac arrhythmias and prolong the QT interval (see Interactions, below).

Patients should be informed about signs and symptoms of hepatitis. Should any of these develop during treatment with telithromycin, they should stop taking the drug and consult their doctor. It should be used with caution in patients with hepatic impairment; however, this is based on limited data in such patients. Reduced doses may be necessary in those with severe renal impairment (see below).

Since telithromycin can produce visual disturbances or loss of consciousness caution is advised when driving, operating machinery, or undertaking similar hazardous activities.

Breast feeding. Telithromycin has been shown to be excreted in the milk of lactating *animals* at concentrations about 5 times greater than those in maternal plasma, although corresponding data for humans is not available.

Pregnancy. Reproductive toxicity, but not teratogenicity, has been seen in *animals*; the potential risk for humans is unknown.

Interactions

Telithromycin is an inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Although there have been few clinical reports, drug interactions with telithromycin may be expected to be similar to those seen with erythromycin (see p.271). In particular, caution is required when telithromycin is given with drugs that may prolong the QT interval. Use of telithromycin with cisapride, ergot alkaloid derivatives, pimozide, astemizole, or terfenadine is usually contra-indicated. Caution is usually necessary with benzodiazepines such as alprazolam, midazolam, and triazolam, and with metoprolol. Telithromycin should not be given with drugs that induce the cytochrome P450 isoenzyme CYP3A4, such as rifampicin, phenytoin, carbamazepine, or St John's wort. Telithromycin increases plasma concentrations of some statins and hence the risk of myopathy; it should not be given with atorvastatin, lovastatin, or simvastatin.

Antimicrobial Action

Telithromycin is a ketolide antibacterial with a bactericidal action and is highly active against certain Gram-positive bacteria, including multidrug-resistant strains of *Streptococcus pneumoniae*. Some strains of *Streptococcus pyogenes* and of *Staphylococcus aureus* are also sensitive.

Telithromycin also shows good activity against the Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*). Activity against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) is comparable with macrolides, and it shows greater activity than erythromycin and roxithromycin against *Legionella* spp. *Mycobacterium* spp. are reported to be moderately susceptible.

Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp. are not susceptible.

◊ References.

1. Hammerschlag MR, *et al.* Activity of telithromycin, a new ketolide antibacterial, against atypical and intracellular respiratory tract pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 25–31.
2. Felmingham D, *et al.* Activity of the ketolide antibacterial telithromycin against typical community-acquired respiratory pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 33–42.
3. Felmingham D, *et al.* Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999-2000). *J Infect* 2004; **48:** 39–55.
4. Drago L, *et al.* Selection of resistance of telithromycin against Haemophilus influenzae, Moraxella catarrhalis and streptococci in comparison with macrolides. *J Antimicrob Chemother* 2004; **54:** 542–5.
5. Farrell DJ, Felmingham D. Activities of telithromycin against 13,874 Streptococcus pneumoniae isolates collected between 1999 and 2003. *Antimicrob Agents Chemother* 2004; **48:** 1882–4.

Pharmacokinetics

Telithromycin is rapidly absorbed after an oral dose, with a bioavailability of 57%. Peak plasma concentrations of about 2 micrograms/mL are reached around 1 to 3 hours after a dose of 800 mg. Food does not affect the absorption of telithromycin.

Telithromycin is widely distributed in body fluids and tissues, including those of the respiratory tract, and plasma protein binding is 60 to 70%. Concentrations in target tissues are reported to be higher than plasma concentrations, suggesting the drug may remain active when the plasma concentration has fallen below the MIC.

About two-thirds of a dose is metabolised in the liver to inactive metabolites and the remaining third is eliminated unchanged in the urine and faeces. Metabolism is mediated both by cytochrome P450 isoenzymes (mainly CYP3A4) and non-cytochrome P450 enzymes. The pharmacokinetics of telithromycin are triphasic with a biphasic elimination phase; the elimination half-life is 2 to 3 hours and the terminal half-life about 10 hours.

Distribution into milk has been found in studies in *animals*.

◊ References.

1. Muller-Serieys C, *et al.* Tissue kinetics of telithromycin, the first ketolide antibacterial. *J Antimicrob Chemother* 2004; **53:** 149–57.
2. Shi J, *et al.* Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. *Clin Pharmacokinet* 2005; **44:** 915–34.
3. Ong CT, *et al.* Intrapulmonary concentrations of telithromycin: clinical implications for respiratory tract infections due to Streptococcus pneumoniae. *Chemotherapy* 2005; **51:** 339–46.

Uses and Administration

Telithromycin is a ketolide antibacterial used for the treatment of susceptible respiratory-tract infections in adults including mild to moderate community-acquired pneumonia. In some countries it is also licensed for use in the treatment of acute sinusitis and acute bacterial exacerbations of chronic bronchitis when resistance to beta-lactam and/or macrolide antibacterials is known or suspected; and as an alternative to beta-lactam antibacterials for tonsillitis or pharyngitis caused by Group A *beta streptococci* in patients over 12 years of age. It is given orally in a usual dose of 800 mg once daily.

Doses may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; **62:** 1771–1804.
2. Zhanel GG, Hoban DJ. Ketolides in the treatment of respiratory infections. *Expert Opin Pharmacother* 2002; **3:** 277–97.
3. Ackermann G, Rodloff AC. Drugs of the 21st century: telithromycin (HMR 3647)—the first ketolide. *J Antimicrob Chemother* 2003; **51:** 497–511.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; **53:** 918–27.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.
6. Wellington K, Noble S. Telithromycin. *Drugs* 2004; **64:** 1683–94.
7. Kasbekar N, Acharya PS. Telithromycin: the first ketolide for the treatment of respiratory infections. *Am J Health-Syst Pharm* 2005; **62:** 905–16.
8. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.
9. Nguyen M, Chung EP. Telithromycin: the first ketolide antimicrobial. *Clin Ther* 2005; **27:** 1144–63.
10. Brown SD. Benefit-risk assessment of telithromycin in the treatment of community-acquired pneumonia. *Drug Safety* 2008; **31:** 561–75.

Administration in renal impairment. Doses of telithromycin should be reduced in severe renal impairment (creatinine clearance of less than 30 mL/minute):

- UK licensed product information states that alternating daily doses of 800 mg and 400 mg, starting with 800 mg may be given whether or not hepatic function is also impaired
- US licensed product information recommends a dose of 600 mg once daily if there is no hepatic impairment but a dose of 400 mg once daily if there is co-existing impairment

Doses should be given after dialysis sessions to patients on haemodialysis.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases (see also Respiratory Disorders, under Uses of Erythromycin, p.273). Ketolides also appear to have such effects: a 10-day course of oral telithromycin 800 mg daily, started with standard treatment for acute asthma (p.1108) in adults, was reported to improve asthma symptoms regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[1] The mechanism of this effect is unclear, however, and further studies are needed.

1. Johnston SL, *et al.* The TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; **354:** 1589–1600.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ketek†; ***Belg.:*** Ketek; ***Braz.:*** Ketek; ***Canad.:*** Ketek; ***Chile:*** Ketek†; ***Cz.:*** Ketek; Levviax†; ***Fin.:*** Ketek; ***Fr.:*** Ketek; ***Ger.:*** Ketek; ***Gr.:*** Ketek; ***Irl.:*** Ketek; ***Ital.:*** Ketek; ***Jpn:*** Ketek; ***Mex.:*** Ketek; ***Neth.:*** Ketek; Levviax†; ***Norw.:*** Ketek; Leviax†; ***Pol.:*** Ketek; ***Port.:*** Ketek; Levviax†; ***S.Afr.:*** Ketek; ***Spain:*** Ketek; Levviax†; ***Swed.:*** Ketek; ***Thai.:*** Ketek; ***Turk.:*** Ketek; ***UK:*** Ketek; ***USA:*** Ketek; ***Venez.:*** Ketek.

Temocillin *(BAN, USAN, rINN)*

Temocilina; Témocilline; Temocillinum. (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.

Темоциллин

$C_{16}H_{18}N_2O_7S_2$ = 414.5.
CAS — 66148-78-5.
ATC — J01CA17.
ATC Vet — QJ01CA17.