and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

For details of doses in infants and children, see below.

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

◊ Reviews.

1. Peters DH, Clissold SP. Clarithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; **44:** 117–64.
2. Barradell LB, *et al.* Clarithromycin: a review of its pharmacological properties and therapeutic use in Mycobacterium avium-intracellulare complex infection in patients with acquired immune deficiency syndrome. *Drugs* 1993; **46:** 289–312.
3. Markham A, McTavish D. Clarithromycin and omeprazole: as Helicobacter pylori eradication therapy in patients with H. pylori-associated gastric disorders. *Drugs* 1996; **51:** 161–78.
4. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; **74:** 613–34.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.

Administration in children. The usual oral dose of clarithromycin for infants and children is 7.5 mg/kg twice daily; those over 12 years of age may be given the usual adult dose (see above).

Although intravenous use is not licensed for children in the UK the *BNFC* suggests a dose of 7.5 mg/kg twice daily for those aged from 1 month to 12 years; older children may be given the adult dose (see above).

For prophylaxis of disseminated infection due to *Mycobacterium avium* complex, clarithromycin may be given in an oral dose of 7.5 mg/kg twice daily; when used for treatment, it should be given with other antimycobacterials and the dose may be increased to 15 mg/kg (to a maximum of 500 mg) twice daily.

For the eradication of *Helicobacter pylori* associated with peptic ulcer disease, the *BNFC* suggests that 7.5 mg/kg twice daily may also be given orally with another antibacterial and a proton pump inhibitor for 7 days to children aged 1 year and over.

Administration in renal impairment. Licensed product information states that in patients with severe renal impairment (creatinine clearance of less than 30 mL/minute) dosage of clarithromycin may need to be halved or the dosing interval doubled.

Ischaemic heart disease. For mention of studies investigating clarithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p.208.

Multiple myeloma. Clarithromycin 500 mg orally twice daily has been added[1] to a regimen of lenalidomide and dexamethasone in treatment-naive patients with multiple myeloma (p.658). The regimen (BiRD) was considered effective and well tolerated, with a higher response rate at lower dexamethasone doses than had been previously reported with lenalidomide and dexamethasone alone. A regimen of clarithromycin, low-dose thalidomide, and dexamethasone (BLT-D) has also been evaluated.[2]

1. Niesvizky R, *et al.* BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood* 2008; **111:** 1101–9.
2. Coleman M, *et al.* BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma* 2002; **43:** 1777–82.

Respiratory disorders. For reference to the use of clarithromycin in the management of respiratory disorders, see under Erythromycin, p.273.

Preparations

USP 31: Clarithromycin Extended-Release Tablets; Clarithromycin for Oral Suspension; Clarithromycin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aeroxina; Centromicina†; Claribiotic; Claricina; Clarimax; Clarimid; Clarovil; Clatromicin†; Corixa; Finasept; Ira; Iset; Kailasa; Klaricid; Klonacid; Macromicina; Orabiot UD†; ***Austral.:*** Clarac; Clarithro; Kalixocin; Klacid; ***Austria:*** Clararcana; Klacid; Maclar; Monocid; ***Belg.:*** Biclar; Heliclar; Maclar; Monaxin†; ***Braz.:*** Clamicin; Claricina†; Clarineo; Claritromax; Claritron†; Clatorin†; Klaricid; Klaritril†; ***Canad.:*** Biaxin; ***Chile:*** Clarimax; Clarosip; Clatic; Euromicina; Infex; Klaricid; Mus†; Pre-Clar; ***Cz.:*** Clarexid; Clarosip; Fromilid; Klabax; Klacid; Lekoklar; Zeclar†; ***Denm.:*** Klacid; ***Fin.:*** Klacid; Zeclar; ***Fr.:*** Mononaxy; Monozeclar; Naxy; Zeclar; ***Ger.:*** Biaxin; Clarithrobeta; Cyllind; Klacid; Mavid; ***Gr.:*** Arecid; Chlamydicin; Claribactron; Clarimex; Claripen; Claromycin; Derizic; Egelif; Eliben; Ezumycin; Geromycin; Glartin; Klaretop; Klaricid; Klarifar; Klarifect; Klarithrin; Klaroxin; Klazidem; Larithro; Laromin; Lyoclar; Macladin; Maxilin; Odycin; Oklaricid†; Pharlemyron; Primocid; Riclemed; Rithroprol; Ritran; Zeclaren; ***Hong Kong:*** Binoclar; Clacin; Cleron; Klacid; Klerimed; Synclar; ***Hung.:*** Cidoclar; Fromilid; Klabax; Klacid; Klamiran†; Klari†; Klarigen; Lekoklar; ***India:*** Bioclar; Clarbact; Claribid; Claricip; Clarimac; Maclar; Synclar; ***Indon.:*** Abbotic; Bicrolid; Binoklar; Clacine; Clapharma; Comtro; Hecobac; ***Irl.:*** Clarosip; Clonocid; Clorom; Klacid; ***Israel:*** Karin; Klacid; Klaridex; ***Ital.:*** Klacid; Macladin; Veclam; ***Jpn:*** Clarith; ***Malaysia:*** Binocular; Crixan; Klacid; Klerimed; Maclar; ***Mex.:*** Adel; Arlecyn-K; Clatrocin; Crolisil; Doycur; Gervaken; Klabet; Klaricid; Klarix; Klarmyn; Klarpharma; Krobicin; Mabicrol; Neo-Clarosip; Quedox; Rolicytin; Torvic; Trimeba; Vikrol; Xuclamin; ***Neth.:*** Clarosip; Klacid; Klaricid; ***Norw.:*** Klacid; ***NZ:*** Clarac; Klacid; ***Philipp.:*** Bysclas; Claranta; Clariget; Klaricid; Klarmyn; Klaz; Larizin; Maxulid; Onexid; ***Pol.:*** Fromilid; Klabax; Klabion; Klacid; Klarmin; Lekoklar; Taclar; ***Port.:*** Ciclinil; Clacina; Clarbac; Clarobiotico; Clarosip; Klacid; Zeclar; ***Rus.:*** Clarbact (Кларбакт); Fromilid (Фромилид); Klabax (Клабакс); Klacid (Клацид); Klaromin (Кларомин); Klerimed (Клеримед); ***S.Afr.:*** Clacee; ClariHexal; Klacid; Klarithran; ***Singapore:*** Clari; Claripen; Cleron; Crixan; Klacid; Klerimed; ***Spain:*** Bremon; Claritur†; Klacid; Kofron; Talicix; ***Swed.:*** Klacid; ***Switz.:*** Claromycine; Klacid; Klaciped; ***Thai.:*** Clarith; Claron; Crixan; Fascar; Klacid; ***Turk.:*** Claricide; Klacid; Klarolid; Klaromin; Klax; Laricid; Macrol; Megacid; Uniklar; ***UAE:*** Clamycin; ***UK:*** Clarosip; Klaricid; ***USA:*** Biaxin; ***Venez.:*** Binoclar; Claranta; Claritic; Claritron; Clarivax; Klaricid.

Multi-ingredient: ***Arg.:*** Heliklar†; ***Austral.:*** Klacid HP 7; Losec Hp 7; Nexium Hp; Pylorid-KA; ***Austria:*** Helipac; ***Braz.:*** Anzopac†; Erradic; H-Bacter; Helicocid Triplice†; Helicopac; Heliklar; Omepramix; Pylorikit; Pyloripac; Pyloritrat; ***Canad.:*** Hp-Pac; Losec 1-2-3 A; Losec 1-2-3 M; ***Fin.:*** Helipak K; ***Ger.:*** ZacPac; ***India:*** OTC HP Kit; Pylokit; ***Malaysia:*** Klacid HP 7; Pylobact Combi; ***Mex.:*** Pylopac; Rezplen; ***Neth.:*** PantoPAC; ***NZ:*** Klacid HP 7†; Losec Hp 7; ***Philipp.:*** OAC Hp7; ***Rus.:*** Pylobact (Пилобакт); ***S.Afr.:*** Losec 20 Triple†; ***Swed.:*** Nexium Hp; ***Turk.:*** Helipak; ***UK:*** Helicleart†; HeliMet†; ***USA:*** Prevpac.

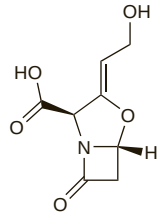
Clavulanic Acid *(BAN, rINN)*

Acide Clavulanique; Ácido clavulánico; Acidum Clavulanicum; BRL-14151; Klavulanik Asit; MM-14151. (*Z*)-(2*R*,5*R*)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Клавулановая Кислота

$C_8H_9NO_5$ = 199.2.

CAS — 58001-44-8 (clavulanic acid); 57943-81-4 (sodium clavulanate).



Potassium Clavulanate *(BANM, rINNM)*

BRL-14151K; Clavulanate de Potassium; Clavulanate Potassium *(USAN)*; Clavulanato potásico; Kalii clavulanas; Kalio klavulanatas; Kaliumklavulanaatti; Kaliumklavulanat; Kálium-klavulanát; Kalium-klavulanát; Potassium, clavulanate de; Potasu klawulanian.

Калия Клавуланат

$C_8H_8KNO_5$ = 237.3.

CAS — 61177-45-5.

NOTE. Compounded preparations of potassium clavulanate may be represented by the following names:

- Co-amoxiclav *x*/*y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

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

Eur. also includes Diluted Potassium Clavulanate.

Ph. Eur. 6.2 (Potassium Clavulanate). The potassium salt of a substance produced by the growth of certain strains of *Streptomyces clavuligerus* or by any other means. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers at a temperature of 2° to 8°.

Ph. Eur. 6.2 (Potassium Clavulanate, Diluted; Kalii Clavulanas Dilutus). A dry mixture of potassium clavulanate and microcrystalline cellulose or anhydrous or hydrated colloidal silicon dioxide. A white or almost white, hygroscopic, powder. A suspension corresponding to 1% of potassium clavulanate in water has a pH of 4.8 to 8.0. Store in airtight containers.

USP 31 (Clavulanate Potassium). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol with decomposition. Stability in aqueous solutions is not good, optimum stability at a pH of 6.0 to 6.3. pH of a 1% solution in water is between 5.5 and 8.0. Store in airtight containers.

Profile

Clavulanic acid is produced by cultures of *Streptomyces clavuligerus*. It has a beta-lactam structure resembling that of the penicillin nucleus, except that the fused thiazolidine ring of the penicillins is replaced by an oxazolidine ring. In general, clavulanic acid has only weak antibacterial activity. It is a potent progressive inhibitor of plasmid-mediated and some chromosomal beta-lactamases produced by Gram-negative bacteria including *Haemophilus ducreyi*, *H. influenzae*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Bacteroides fragilis*, and some Enterobacteriaceae. It is also an inhibitor of the beta-lactamases produced by *Staphylococcus aureus*. Clavulanic acid can permeate bacterial cell walls and can therefore inactivate both extracellular enzymes and those that are bound to the cell. Its mode of action depends on the particular enzyme inhibited, but it generally acts as a competitive, and often irreversible, inhibitor. Clavulanic acid consequently enhances the activity of penicillin and cephalosporin antibacterials against many resistant strains of bacteria. However, it is generally less effective against chromosomally mediated type 1 beta-lactamases; therefore, many *Citrobacter*, *Enterobacter*, *Morganella*, and *Serratia* spp., and *Pseudomonas aeruginosa* remain resistant. Some plasmid-mediated extended-spectrum beta-lactamases in *Klebsiella pneumoniae*, some other Enterobacteriaceae, and *Ps. aeruginosa* are also not inhibited by beta-lactamase inhibitors.

Clavulanic acid is given as potassium clavulanate orally and by injection with amoxicillin (co-amoxiclav) (p.202), and by injection with ticarcillin (p.352).

Use of clavulanate with penicillins has been associated with the development of cholestatic jaundice and hepatitis (see under Adverse Effects of Amoxicillin, p.202) and therefore the use of co-amoxiclav has declined (see below).

◊ Because of the risk of cholestatic jaundice co-amoxiclav is not a treatment of choice for common bacterial infections. The UK CSM[1] recommended that it should be reserved for bacterial infections likely to be caused by amoxicillin-resistant beta-lactamase-producing strains and that treatment should not usually exceed 14 days. It may be considered for the following main indications:

- sinusitis, otitis media, recurrent tonsillitis
- acute exacerbations of chronic bronchitis
- bronchopneumonia
- urinary-tract infections, especially when recurrent or complicated, but not prostatitis
- septic abortion, pelvic or puerperal sepsis, and intra-abdominal sepsis
- cellulitis, animal bites, and severe dental abscess with spreading cellulitis.

1. Committee on Safety of Medicines/Medicines Control Agency. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Preparations

BP 2008: Co-amoxiclav Injection; Co-amoxiclav Tablets;
USP 31: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Optamox; ***Indon.:*** Aclam; ***Turk.:*** Amoksilav.

Multi-ingredient: ***Arg.:*** Aclav; Amixen Clavulanico; Amoclav; Amoxi Plus; Amoxigrand Compuesto; Amoxitenk Plus; Bi Moxal; Bi Moxal Duo; Bioclavid; Bioxilina Plus; Clavulox; Clavulox Duo; Cloximar Duo; Darzitil Plus; Dibional; Fullcilina Plus†; Grinsil Clavulanico; Klonalmox; ***Austral.:*** Augmentin; Ausclav†; Clamohexal; Clamoxyl; Clavulin; Curam; Timentin; ***Austria:*** Amoclan; Amoxicillin comp; AmoxiClavulan; Amoxicomp; Amoxiplus; Amoxistad plus; Augmentin; Benclav; Benomox; Betamoclav; Clavamox; Clavex; Clavolek; Clavoplus; Clavulanex; CombAmox; Curam; Lanoclav; Lekamoxiclav; Oxyclav; Xiclav; ***Belg.:*** Amoclane; Augmentin; Clavucid; Co-Amoxi; Co-Amoxilan†; Docamoclaf; Timentin; ***Braz.:*** Augmentin; Betaclav; Clav-Air†; Clavoxil†; Clavulin; Novamox; Policlavumoxil; Sigma Clav; Timentin; ***Canad.:*** Apo-Amoxi Clav; Clavulin; Novo-Clavamoxin; ratio-Aclavulanate; Timentin; ***Chile:*** Ambilan; Ambilan Bid; Amolex; Augmentin; Augmentin Bid; Clavinex; Clavinex Duo; Clavoxilina Bid; ***Cz.:*** Amoksiklav; Augmentin; Augmentin-Duo; Betaklav; Curam; Enhancin; Forcid; Klamoxin†; Megamox; Timentin; ***Denm.:*** Bioclavid; Spektramox; ***Fin.:*** Amoxin Comp; Augmentin; Bioclavid; Clapharin Comp; Clavurion; Clavuxal; Forcid; Spektramox†; ***Fr.:*** Augmentin; Ciblor; Claventin; ***Ger.:*** Abiclav; Amoclav; Amoxclav; Amoxi-Clavulan; Amoxi-saar plus; Amoxicillin comp; Amoxiclav; Amoxidura Plus; Amoxillat-Clav†; Amuclan†; Augmentan; ***Gr.:*** Augmentin; Bioclavid; Forcid; Frolicin; Fugentin; Moxiclav; Tenervan; Timentin; ***Hong Kong:*** Amoksiklav; Augmentin; Clamovid; Curam; Fleming; Moxiclav; Qualimentin; Timentin; ***Hung.:*** Aktil; Amoclan†; Amoclav; Augmentin; Augmentin-Duo; Augmentin-Extra; Clavumox†; Co-Amoxi; Curam; Enhancin; Forcid; ***India:*** Augmentin; Boostim; Novaclav; Nuclav; Rapiclav†; Timentin; ***Indon.:*** Amocomb; Ancla; Augmentin; Auspilic; Bellamox; Betaclav; Biditin; Capsinat; Clabat; Claneksi; Clavamox; Comsikla; Danoclav; Daxet; Dexyclav; Improvox; Lansiclav; Nufaclav; Nuvoclav; Prafamoc; Protamox; Surpas; Syneclav; Viaclav; Vulamox; Zumafen; ***Irl.:*** Augmentin; Clavamel; Germentin; Pinaclav; Timentin†; ***Israel:*** Amoxiclav; Augmentin; Clavamox; Timentin; ***Ital.:*** Abba; Anival; Augmentin; Clavucar†; Clavulin; Neoduplamox; Timentin; Xinamod; ***Malaysia:*** Augmentin; Cavumox; Clamovid; Curam; Enhancin; Moxiclav; Vestaclav†; ***Mex.:*** Acarbixin; Acimox AC; Alvi-Tec; Amobay CL; Amoxiclav; Amoxiclide; Apoclavox; Augmentin; Auvuxilan; Clambusil; Clamoxin; Clavant; Clavucyd; Clavulin; Clavuser; Enhancin; Gramaxin; Maxint†; Moxlin CLV; Riclasip; Servamox CLV; Sinufin; Timentin; Valclan; ***Neth.:*** Amoclan; Amuclan; Augmentin; Bioclavid; Forcid; Timentin; ***Norw.:*** Bremide†; ***NZ:*** Alpha-Amoxyclav; Augmentin; Synermox; Timentin; ***Philipp.:*** Amoclav; Augmentin; Augmex; Augurcin; Bactiv; Bactoclav; Bioclavid; Clamovid; Claneksi; Claventin; Clavoxel; Clovimax; Enhancin; Exten; Klavic; Natravox; Proxiclav; Sullivan; Suplentin; Timentin; Valmocel; Xilanic; ***Pol.:*** Amoksiklav; Augmentin; Curam; Forcid; Ramoclav; Taromentin; Timentin; ***Port.:*** Amoclavam; Amplamox Plus; Augmentin; Betamox; Clavamox; Clavepen; Forcid; Noprilam; Penilan; ***Rus.:*** Amoclan (Амоклан); Amoksiklav (Амоксиклав); Augmentin (Аугментин); Flemoclav (Флемоклав); Medoclav (Медоклав); Panklav (Панклав); Rapiclav (Рапиклав); Timentin (Тиментин); ***S.Afr.:*** Adco-Amoclav; Augmaxcil; Augmentin; Bio-Amoksiclav; Clamentin; Clavumox; Co-Amoxyclav; Curam; Forcid; Moxyclav†; Ranclav; Rolab-Amoclav; ***Singapore:*** Amocla; Augmentin; Augmex†; Clamonex; Clamovid; Curam; Enhancin; Fugentin; Moxiclav; ***Spain:*** Amoclave; Amoxyplus; Ardineclav; Augmentine; Bigpen†; Burmicin; Clavepen; Clavucid; Clavumox; Duonasa; Eupeclanic†; Inmupen†; Kelsopen; ***Swed.:*** Bioclavid; Spektramox; ***Switz.:*** Amicosol; Augmentin; Aziclav; Clavamox; clavu-basan†; Co-Amoxi; Co-Amoxicilline; Timenten†; ***Thai.:*** Amocla; Amoksiklav; Augclav; Augmentin; Augpen; Cavumox; Curam; Klamoks; Moxiclav; Moxicle; Pencla; Ranclav; ***Turk.:*** Amoklavin; Augmentin; Bioment; Croxilex; Klamoks; Klavunat; Klavupen; ***UAE:*** Julmentin; ***UK:*** Amiclav†; Augmentin; Augmentin-Duo; Timentin; ***USA:*** Amoclan; Augmentin; Timentin; ***Venez.:*** Augmentin; Augmentin Bid†; Clavumox; Curam; Fulgram.