maturia, and proteinuria. The effect of the formaldehyde may be reduced by alkalinising drugs, such as sodium bicarbonate, or large quantities of water, but it is then less effective.

Methenamine and its salts are contra-indicated in patients with hepatic impairment because of the liberation of ammonia in the gastrointestinal tract. Although methenamine itself is not contra-indicated in renal impairment, its salts should be avoided in severe impairment because of the risk of mandelate or hippurate crystalluria. They should also be avoided in patients with severe dehydration, metabolic acidosis, or gout.

Interference with laboratory estimations for catecholamines, 17-hydroxycorticosteroids, and oestrogens in the urine has been reported.

Interactions

The use of drugs that alkalinise the urine, including some antacids, potassium citrate, and diuretics such as acetazolamide or the thiazides, should be avoided because the activation of methenamine to formaldehyde may be inhibited (but see above).

Use of methenamine with sulfonamides may increase the risk of crystalluria since methenamine requires low urinary pH for its effect, at which sulfonamides and their metabolites are poorly soluble; methenamine may also form poorly soluble compounds with some sulfonamides.

Antimicrobial Action

Methenamine owes its antibacterial properties to formaldehyde, a non-specific bactericide, which is slowly liberated by hydrolysis at acid pH. Most Gram-positive and Gram-negative organisms and fungi are susceptible. Hippuric and mandelic acids have some antibacterial activity *in vitro*, but their contribution to the antibacterial action of the salts *in vivo*, beyond assisting the maintenance of low urinary pH, is uncertain. Urea-splitting organisms such as *Proteus* and some *Pseudomonas* spp. tend to increase urinary pH and inhibit the release of formaldehyde, thereby decreasing the effectiveness of methenamine. Use with acetohydroxamic acid, a potent inhibitor of bacterial urease, has been suggested for urinary infections due to these organisms. True resistance to formaldehyde does not appear to be a problem in clinical use.

Pharmacokinetics

Methenamine is readily absorbed from the gastrointestinal tract and widely distributed in the body. Under acid conditions methenamine is slowly hydrolysed to formaldehyde and ammonia: about 10 to 30% of an oral dose may be converted in the stomach unless it is given as an enteric-coated preparation. Almost no hydrolysis of methenamine takes place at physiological pH, and it is therefore virtually inactive in the body. The half-life is reported to be about 4 hours. Methenamine is rapidly and almost completely eliminated in the urine, and provided this is acidic (preferably below pH 5.5) bactericidal concentrations of formaldehyde are achieved. Because of the time taken for hydrolysis, however, these are not achieved until the urine reaches the bladder, with peak concentrations occurring up to 2 hours after an oral dose. Absorption, and hence excretion, may be somewhat delayed in patients given enteric-coated formulations.

Methenamine crosses the placenta and small amounts may be distributed into breast milk.

The mandelate and hippurate moieties are also rapidly absorbed and are excreted in urine by tubular secretion as well as glomerular filtration.

Uses and Administration

Methenamine is used, usually as the hippurate or mandelate, in the prophylaxis and treatment of chronic or recurrent, uncomplicated, lower urinary-tract infections and asymptomatic bacteriuria. It has been considered suitable for long-term use because acquired resistance does not appear to develop.

Methenamine and its salts should not be used in upper urinary-tract infections because it is eliminated too rapidly to exert an effect, nor in acute urinary infections. It is only active in acidic urine, when formaldehyde is released, and although hippuric or mandelic acid helps to acidify the urine, ammonium chloride or ascorbic acid may be tried. If urea-splitting bacteria such as *Proteus* or some *Pseudomonas* spp. are present they may produce so much ammonia that the urine cannot be acidified (see also Antimicrobial Action, above).

The usual oral adult dose of methenamine or methenamine mandelate is 1 g given four times daily. Methenamine hippurate is given orally in a usual dose of 1 g twice daily; the dose may be increased to three times daily in catheterised patients.

For details of doses in children, see below.

Methenamine has been used topically in deodorant preparations, since in the presence of acid sweat it liberates formaldehyde. Methenamine calcium thiocyanate has been used in combination preparations for upper respiratory-tract disorders.

◊ Reviews.

1. Schiøtz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand* 2002; **81:** 743–6.
2. Lee BB, *et al.* Methenamine hippurate for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 11/01/08).

Administration in children. In the USA, the usual recommended oral dose of methenamine mandelate in children up to 6 years old is about 18 mg/kg given four times daily; those aged 6 to 12 years may be given methenamine or methenamine mandelate 500 mg four times daily.

In the UK, methenamine hippurate may be given in a usual oral dose of 500 mg twice daily in children aged 6 to 12 years. Doses of up to 1 g twice daily have been given in the USA.

Preparations

USP 31: Methenamine Elixir; Methenamine Hippurate Tablets; Methenamine Mandelate Delayed-release Tablets; Methenamine Mandelate for Oral Solution; Methenamine Mandelate Oral Suspension; Methenamine Mandelate Tablets; Methenamine Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Hiprex; ***Austria:*** Hiprex; ***Belg.:*** Hiprex†; ***Canad.:*** Dehydral; Hiprex; Mandelamine; Urasal†; ***Denm.:*** Geasalol†; Haiprex; ***Fin.:*** Hipeksal; Hiprex; ***Ger.:*** Antihydral; Urotractan; ***Irl.:*** Hiprex†; ***Israel:*** Hiprex; ***Mex.:*** Bioran; ***Neth.:*** Reflux; ***Norw.:*** Hiprex; ***NZ:*** Hiprex; ***Philipp.:*** Hiprex; ***Pol.:*** Stoppot; ***S.Afr.:*** Hippramine†; Mandelamine†; ***Swed.:*** Hiprex; ***Switz.:*** Antihydral; ***Turk.:*** Helpa; Hippurin; Manuprin; Neturone; Purinol; Uron; ***UK:*** Hiprex; ***USA:*** Hiprex; Mandelamine; Urex; ***Venez.:*** Mandelamine.

Multi-ingredient: ***Arg.:*** Calculina†; ***Belg.:*** Carbobel; Mictasol-P; Mictasol†; ***Braz.:*** Abacateirol†; Acridin; Cystex; Sepurin; Urodonal†; ***Chile:*** Uroknop; ***Fr.:*** Mictasol; Pedi-Relax Anti-Transpirant; ***Ger.:*** Antihydral M†; ***Hong Kong:*** Antihydral M†; ***Hung.:*** Bilagit†; ***Mex.:*** Furanton†; ***Pol.:*** Dezorol; Pedipur; Urosal; ***Turk.:*** Helmobleu; ***USA:*** Atrosept; Cystex; Dolsed†; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X†; UAA; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira; ***Venez.:*** Azo-Mandelamine.

Meticillin Sodium *(rINNM)*

BRL-1241; Dimethoxyphenecillin Sodium; Dimethoxyphenyl Penicillin Sodium; Methicillin Sodium *(BANM, USAN)*; Meticilina sódica; Méticilline Sodique; Meticillinum Natricum; Natrii Meticillinum; SQ-16123; X-1497. Sodium (6*R*)-6-(2,6-dimethoxybenzamido)penicillanate monohydrate.

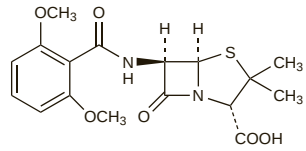
Натрий Метициллин

$C_{17}H_{19}N_2NaO_6S,H_2O$ = 420.4.

CAS — 61-32-5 (meticillin); 132-92-3 (anhydrous meticillin sodium); 7246-14-2 (meticillin sodium monohydrate).

ATC — J01CF03.

ATC Vet — QJ01CF03.



(meticillin)

Incompatibility. Meticillin sodium has been reported to be incompatible with aminoglycosides and a number of other antimicrobials. It has also been reported to be incompatible with acidic and alkaline drugs.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Meticillin is the penicillin most commonly associated with acute interstitial nephritis.

Effects on the kidneys. References.

1. Sanjad SA, *et al.* Nephropathy, an underestimated complication of methicillin therapy. *J Pediatr* 1974; **84:** 873–7.
2. Galpin JE, *et al.* Acute interstitial nephritis due to methicillin. *Am J Med* 1978; **65:** 756–65.

Sodium content. Each g of meticillin sodium contains about 2.4 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Meticillin has a mode of action similar to that of benzylpenicillin (p.214) but it is resistant to staphylococcal penicillinase. There is evidence that meticillin is more stable to staphylococcal penicillinase than the other penicillinase-resistant penicillins.

Meticillin is active against both penicillinase-producing and non-penicillinase-producing staphylococci, and also against *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Str. pneumoniae*, and some viridans streptococci. Its activity against penicillin-sensitive staphylococci and streptococci is less than that of benzylpenicillin. It is virtually ineffective against *Enterococcus faecalis*.

Resistance of staphylococci to meticillin is due to the expression of an altered penicillin-binding protein and is not dependent on penicillinase production. There is cross-resistance with other penicillins, including the penicillinase-resistant penicillins cloxacillin, dicloxacillin, flucloxacillin, nafcillin, and oxacillin, and with the cephalosporins. Meticillin-resistant staphylococci are also frequently resistant to other antibacterials, including aminoglycosides, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, and tetracycline. The incidence of such resistance has varied considerably. However, both endemic (restricted to one hospital) and epidemic (affecting more than one hospital) strains of meticillin-resistant *Staphylococcus aureus* (MRSA) are now recognised and infections are a problem in many hospitals.

There have been fewer studies on coagulase-negative staphylococci, but patterns of meticillin resistance in *Staph. epidermidis* are similar to those for MRSA and the frequency of resistance may be higher.

For further details on meticillin-resistant staphylococci and the management of infections, see under Staphylococcal Infections, p.195.

Resistance. References to meticillin-resistant staphylococci.

1. Hackbarth CJ, Chambers HF. Methicillin-resistant staphylococci: genetics and mechanisms of resistance. *Antimicrob Agents Chemother* 1989; **33:** 991–4.
2. Maple PAC, *et al.* World-wide antibiotic resistance in methicillin-resistant Staphylococcus aureus. *Lancet* 1989; **i:** 537–40.
3. Mouton RP, *et al.* Correlations between consumption of antibiotics and methicillin resistance in coagulase negative staphylococci. *J Antimicrob Chemother* 1990; **26:** 573–83.
4. Marples RR, Reith S. Methicillin-resistant Staphylococcus aureus in England and Wales. *Commun Dis Rep* 1992; **2:** R25–R29.
5. de Lencastre H, *et al.* Molecular aspects of methicillin resistance in Staphylococcus aureus. *J Antimicrob Chemother* 1994; **33:** 7–24.
6. Fluckiger U, Widmer AF. Epidemiology of methicillin-resistant Staphylococcus aureus. *Chemotherapy* 1999; **45:** 121–34.
7. Livermore DM. Antibiotic resistance in staphylococci. *Int J Antimicrob Agents* 2000; **16** (suppl 1): S3–S10.
8. Turnidge JD, Bell JM. Methicillin-resistant Staphylococcal aureus evolution in Australia over 35 years. *Microb Drug Resist* 2000; **6:** 223–9.

Pharmacokinetics

Meticillin is inactivated by gastric acid and must be given by injection. Peak plasma concentrations are attained within 0.5 to 1 hour of an intramuscular injection; concentrations of up to 18 micrograms/mL have been achieved after a dose of 1 g. A half-life of 0.5 to 1 hour has been reported, although this may be increased to 3 to 6 hours in renal impairment. About 40% of the meticillin in the circulation is bound to plasma proteins. It is widely distributed in body fluids and in tissues, but there is little diffusion into the CSF unless the meninges are inflamed. Meticillin also crosses the placenta and appears in breast milk. Relatively high concentrations are achieved in bile compared with plasma, although only small amounts are excreted in bile. The majority is rapidly excreted by tubular secretion and glomerular filtration; up to 80% of an injected dose has been detected unchanged in the urine.

Plasma concentrations are enhanced by probenecid. They may be reduced in patients with cystic fibrosis.

Uses and Administration

Meticillin is a penicillinase-resistant penicillin and has been used similarly to flucloxacillin (p.277) in the treatment of staphylococcal infections resistant to benzylpenicillin. It is not active orally and has been given by injection as the sodium salt.

Mezlocillin *(BAN, USAN, rINN)*

Metslosilliini; Mezlocilina; Mezlocilline; Mezlocillinum. 6-[*N*-(3-Methylsulfonyl-2-oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

Мезлоциллин

$C_{21}H_{25}N_5O_8S_2$ = 539.6.

CAS — 51481-65-3.

ATC — J01CA10.

ATC Vet — QJ01CA10.

Mezlocillin Sodium *(BANM, rINNM)*

Bay-f-1353; Mezlocilina sódica; Mezlocilline Sodique; Natrii Mezlocillinum. Sodium (6*R*)-6-[D-2-(3-mesyl-2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate monohydrate.

Натрий Мезлоциллин

$C_{21}H_{24}N_5NaO_8S_2,H_2O$ = 579.6.

CAS — 42057-22-7 (anhydrous mezlocillin sodium); 80495-46-1 (mezlocillin sodium monohydrate).

ATC — J01CA10.

ATC Vet — QJ01CA10.

Pharmacopoeias. In *US*.

USP 31 (Mezlocillin Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 4.5 and 8.0. Store in airtight containers.

Incompatibility. Mezlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Prolongation of bleeding time has been less frequent and less severe with mezlocillin than with carbenicillin.

Sodium content. Each g of mezlocillin sodium contains about 1.7 mmol of sodium. As mezlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions
As for Benzylpenicillin, p.214.

Cefotaxime. For the effect of mezlocillin on the clearance of cefotaxime, see p.228.

Antimicrobial Action
Mezlocillin has a similar antimicrobial action to piperacillin (p.315). Its activity against *Pseudomonas aeruginosa* is less than that of azlocillin or piperacillin.

Pharmacokinetics
Mezlocillin is not absorbed from the gastrointestinal tract to any significant extent. It is well absorbed after intramuscular injection, with peak plasma concentrations of 15 to 25 micrograms/mL 45 to 90 minutes after a single dose of 1 g. It is reported to have nonlinear dose-dependent pharmacokinetics. Between 16 and 42% of mezlocillin in the circulation is bound to plasma proteins. Mezlocillin is reported to have a plasma half-life of about 1 hour; this is slightly prolonged in neonates, and in patients with renal impairment half-lives of up to about 6 hours have been reported.

Mezlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into CSF except when the meninges are inflamed.

Mezlocillin is reported to be metabolised to a limited extent. About 55% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 6 hours of a dose, hence achieving high urinary concentrations. High concentrations are also found in the bile; up to 30% of a dose has been reported to be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Mezlocillin is removed by haemodialysis, and to some extent by peritoneal dialysis.

Uses and Administration
Mezlocillin is a ureidopenicillin with uses similar to those of piperacillin (p.316). It is commonly used with an aminoglycoside; however they should be given separately as they have been shown to be incompatible.

Administration and dosage. Mezlocillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of mezlocillin; 1.07 g of mezlocillin sodium is equivalent to about 1 g of mezlocillin. Dosage may need to be reduced in renal impairment. It may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 30 minutes, or by deep intramuscular injection. Single intramuscular doses should not exceed 2 g.

For the treatment of serious infections, 200 to 300 mg/kg daily in divided doses may be given intravenously. For life-threatening infections, up to 350 mg/kg daily may be used, but the total daily dose should not normally exceed 24 g. For uncomplicated urinary-tract infections, a dose of 1.5 to 2 g may be given intramuscularly or intravenously every 6 hours.

Uncomplicated gonorrhoea may be treated by a single intramuscular or intravenous dose of mezlocillin 1 to 2 g. Probenecid 1 g orally may be given at the same time or up to 30 minutes before the injection.

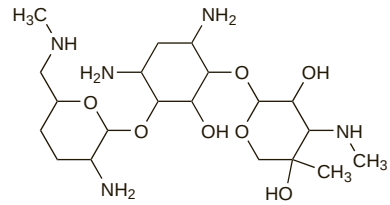
For the prophylaxis of infection during surgery, an intravenous pre-operative dose of mezlocillin 4 g, repeated at 6-hourly intervals for 2 further doses, may be given.

Preparations
USP 31: Mezlocillin for Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Baypen; ***Fr.:*** Baypen; ***Ger.:*** Baypen; ***Israel:*** Baypen†; ***Ital.:*** Baypen.
Multi-ingredient: ***Ger.:*** Optocillin†.

Micronomicin Sulfate *(pINNM)*
Gentamicin C_{2B} Sulphate; KW-1062 (micronomicin); 6′*N*-Methylgentamicin C_{1A} Sulphate; Micronomicin Sulphate; Micronomicine, Sulfate de; Micronomicini Sulfas; Sagamicin Sulphate; Sulfato de micronomicina. *O*-2-Amino-2,3,4,6-tetradeoxy-6-(methylamino)-*α*-D-*erythro*-hexopyranosyl-(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)]-2-deoxy-D-streptamine hemipentasulphate.

Микрономицина Сульфат
$(C_{20}H_{41}N_5O_7)_2,5H_2SO_4$ = 1417.5.
CAS — 52093-21-7 (micronomicin).
ATC — S01AA22.
ATC Vet — QS01AA22.



(micronomicin)

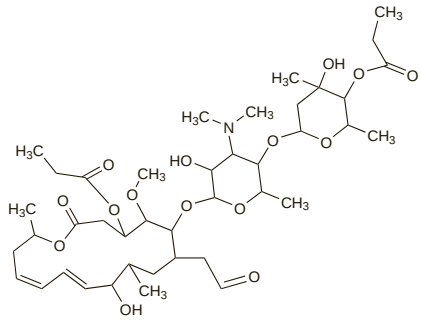
Pharmacopoeias. In *Chin.* and *Jpn*.

Profile
Micronomicin is an aminoglycoside with general properties similar to those of gentamicin (p.282). It is given as the sulfate and doses are expressed in terms of micronomicin; 183 mg of micronomicin sulfate is equivalent to about 120 mg of micronomicin. It is given by intramuscular injection or by intravenous infusion over 30 minutes to 1 hour in doses of 120 to 240 mg daily in 2 or 3 divided doses. Dosage should be adjusted based on serum-micronomicin concentration monitoring. It is also used topically as eye drops or ointment in a concentration of 0.3% for infections of the eye.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Luxomicina; ***Jpn:*** Sagamicin; ***Singapore:*** Sagamicin†.

Midecamycin *(rINN)*
Midecamicina; Midecamycin A_1; Midécamycine; Midecamycinum; Mydecamycin. 7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′,4″-dipropionate.

Мидекамицин
$C_{41}H_{67}NO_{15}$ = 814.0.
CAS — 35457-80-8.
ATC — J01FA03.
ATC Vet — QJ01FA03.



Pharmacopoeias. In *Jpn*.

Midecamycin Acetate *(rINNM)*
Acecamycin; Acetato de midecamicina; Midecamycin Diacetate; Midécamycine, Acétate de; Midecamycini Acetas; Miocamycin; Miokamycin; MOM; Ponsinomycin; 1532-RB. 9,3″-Diacetylmidecamycin; Leucomycin V 3^B, 9-diacetate $3,4^B$-dipropanoate.

Мидекамицина Ацетат
$C_{45}H_{71}NO_{17}$ = 898.0.
CAS — 55881-07-7.
ATC — J01FA11.
ATC Vet — QJ01FA11.

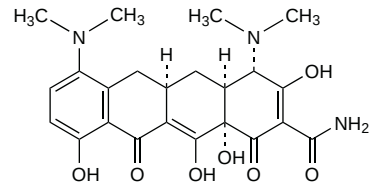
Pharmacopoeias. In *Jpn*.

Profile
Midecamycin is a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens* with actions and uses similar to those of erythromycin (p.269) but it is somewhat less active. It is given orally for the treatment of susceptible infections as the acetate in usual doses of 0.9 to 1.8 g daily in 2 or 3 divided doses. It has also been given as the base.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Myoxam†; ***Belg.:*** Merced; ***Fr.:*** Mosil; ***Gr.:*** Miocacin; Miocamen; ***Hong Kong:*** Medemycin; ***Ital.:*** Macroral; Midecin; Miocamen; Miokacin; ***Jpn:*** Medemycin; Miocamycin; ***Mex.:*** Midecamin†; ***Port.:*** Miocacin; ***Rus.:*** Macropen (Макропен); ***Spain:*** Momicine; Myoxam; Normicina†; ***Thai.:*** Miotin.

Minocycline *(BAN, USAN, rINN)*
Minociclina; Minocyclinum; Minocyklin; Minosiklin; Minosykliini. (4*S*,4a*S*,5a*R*,12a*S*)4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-7-dimethylaminotetracycline.

Миноциклин
$C_{23}H_{27}N_3O_7$ = 457.5.
CAS — 10118-90-8;.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.



Minocycline Hydrochloride *(BANM, rINNM)*
Hidrocloruro de minociclina; Minociklin-hidroklorid; Minociklino hidrochloridas; Minocycline, chlorhydrate de; Minocyclini hydrochloridum; Minocyklin-hydrochlorid; Minocyklinhydroklorid; Minocykliny chlorowodorek; Minosykliinihydrokloridi.

Миноциклина Гидрохлорид
$C_{23}H_{27}N_3O_7,HCl$ = 493.9.
CAS — 13614-98-7.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Minocycline Hydrochloride Dihydrate). A yellow, hygroscopic, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.
USP 31 (Minocycline Hydrochloride). A yellow crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of minocycline 1% is between 3.5 and 4.5. Store in airtight containers. Protect from light.

Incompatibility. Preparations of minocycline hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Adverse Effects and Precautions
As for Tetracycline, p.347.

Gastrointestinal disturbances with minocycline are reported to be less frequent than with the less well absorbed tetracyclines.

Oesophageal ulceration has occurred and may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: minocycline should be taken with at least half a glass of water, in an upright position, and well before going to bed.

Vestibular adverse effects including dizziness or vertigo may occur with minocycline, particularly in women. Patients should be advised not to drive or operate machinery if affected. Tinnitus and decreased hearing have been reported rarely.

There have also been reports, some fatal, of a hypersensitivity syndrome (comprising eosinophilia, fever, rash, and varying additional symptoms), a lupus-like syndrome, and a serum-sickness-like syndrome (both comprising arthralgia, fever, and joint stiffness or swelling, amongst other symptoms).

Minocycline may also cause hyperpigmentation of the skin (see below).