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

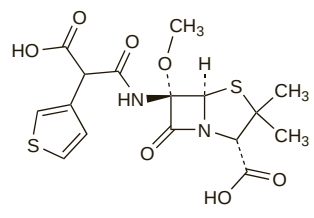
Proprietary Preparations (details are given in Part 3)
Arg.: Ketek†; ***Belg.:*** Ketek; ***Braz.:*** Ketek; ***Canad.:*** Ketek; ***Chile:*** Ketek†; ***Cz.:*** Ketek; Levviax†; ***Fin.:*** Ketek; ***Fr.:*** Ketek; ***Ger.:*** Ketek; ***Gr.:*** Ketek; ***Irl.:*** Ketek; ***Ital.:*** Ketek; ***Jpn:*** 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.



Temocillin Sodium *(BANM, rINNM)*

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Témocilline Sodique. The disodium salt of (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.

Натрий Темоциллин

$C_{16}H_{16}N_2Na_2O_7S_2$ = 458.4.

CAS — 61545-06-0.

ATC — J01CA17.

ATC Vet — QJ01CA17.

Profile

Temocillin is a semisynthetic penicillin that is highly resistant to a wide range of beta-lactamases and is used for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative aerobic bacteria, including those resistant to third-generation cephalosporins.

It is given as the sodium salt and doses are expressed in terms of the base; 1.11 g of temocillin sodium is equivalent to about 1 g of temocillin. It is given by intravenous or intramuscular injection or by intravenous infusion in usual doses of 1 g every 12 hours. A dose of 12.5 mg/kg every 12 hours may be used in children. Intravenous doses may be doubled in severe infections.

In patients with renal impairment the interval between doses may need to be increased.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Negaban; ***Ital.:*** ISF 09338†; ***UK:*** Negaban.

Terizidone *(rINN)*

B-2360; Terizidona; Térizidone; Terizidonum. 4,4′-[*p*-Phenylenebis(methyleneamino)]bis(isoxazolidin-3-one).

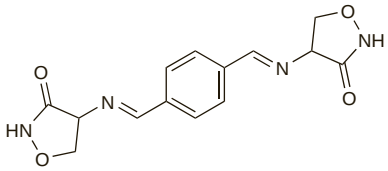
Теризидон

$C_{14}H_{14}N_4O_4$ = 302.3.

CAS — 25683-71-0.

ATC — J04AK03.

ATC Vet — QJ04AK03.



Profile

Terizidone has been used in the treatment of infections of the urinary tract and of pulmonary and extrapulmonary tuberculosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Terivalidin; ***Braz.:*** Terizidex; ***S.Afr.:*** Terivalidin.

Tetracycline *(BAN, rINN)*

Tetraciclina; Tetraciklin; Tetraciklinas; Tétracycline; Tetracyclinum; Tetracyklin; Tetracyklina; Tetrasykliini. A variably hydrated form of (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide.

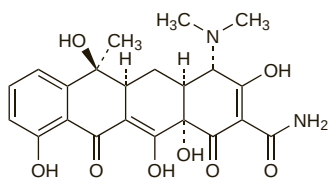
Тетрациклин

$C_{22}H_{24}N_2O_8$ = 444.4.

CAS — 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate).

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QG01AA90; QG51AA02; QJ01AA07; QJ51AA07; QS01AA09; QS02AA08; QS03AA02.



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

Ph. Eur. 6.2 (Tetracycline). A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

USP 31 (Tetracycline). A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Tetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tetraciclina; Tetraciklinhidroklorid; Tetraciklino hidrochloridas; Tétracycline, chlorhydrate de; Tetracyclini hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi.

Тетрациклина Гидрохлорид

$C_{22}H_{24}N_2O_8$,HCl = 480.9.

CAS — 64-75-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

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

US also includes Epitetracycline Hydrochloride.

Ph. Eur. 6.2 (Tetracycline Hydrochloride). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

USP 31 (Tetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light.

Tetracycline Phosphate Complex *(BAN)*

Tetraciclina, complejo con fosfato.

CAS — 1336-20-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

Description. A complex of sodium metaphosphate and tetracycline.

Incompatibility. Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Tetracycline undergoes reversible epimerisation in *solution* to the less active 4-epitetracycline;[1,2] the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.[1] The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.[1] Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose about 8 to 12% of their potency in 24 hours at room temperature.[3] Although epimerisation has been observed to be the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.[4]

In contrast to the case in solution, *suspensions* of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.[2] This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of *solid* dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37° and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.[5] Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.[5] However, although this study, and an accelerated stability study carried out by WHO[6] indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.[7]

1. Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; **52:** 752–6.
2. Grobben-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; **7:** 104–8.
3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; **24:** 434–9.
4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; **6:** 201–14.
5. Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; **59:** 1160–4.
6. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 18/05/07)
7. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–14.

Adverse Effects

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Oesophageal ulceration has been reported with doxycycline, minocycline, and tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime. Other effects that have been reported include glossitis, stomatitis, and dysphagia.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed derivatives such as doxycycline.

Renal dysfunction has been reported with tetracyclines, particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal impairment increase the severity of uraemia with increased excretion of nitrogen and loss of sodium, accompanied by acidosis and hyperphosphataemia, and may lead to excessive systemic accumulation of the tetracycline and possible liver toxicity. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and interstitial nephritis have occurred rarely.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women and in patients with renal impairment or those given high doses. However, hepatotoxicity has also occurred in patients without these predisposing factors but is rarely reported with doxycycline.

Tetracyclines are deposited both in deciduous teeth (milk teeth; primary teeth) and in permanent teeth during their formation, causing permanent discoloration and enamel hypoplasia. The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose given. Doxycycline binds less with calcium compared with other tetracyclines and these changes may occur less frequently. Tetracyclines are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women.

Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances, and papilloedema has been reported. The use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracra-