It is given topically as the sulfate for the treatment of eye infections. It has also been given intramuscularly and orally. It is reported to be more toxic than kanamycin.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Kanacyl†.

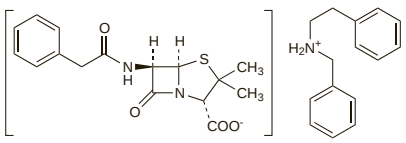
Multi-ingredient: ***Ital.:*** Visucloben Antibiotico; Visumetazone Antibiotico.

Benethamine Penicillin *(BAN, rINN)*

Bénéthamine Pénicilline; Benethaminum Penicillinum; Penicilinabenetamina. Benzyl(phenethyl)ammonium (6*R*)-6-(2-phenylacetamido)penicillanate.

Бенетамин Пенициллин

$C_{15}H_{17}N,C_{16}H_{18}N_2O_4S$ = 545.7.
CAS — 751-84-8.



Profile

Benethamine penicillin is a poorly soluble derivative of benzylpenicillin (p.213) with similar actions and uses, although it is not recommended for chronic, severe, or deep-seated infections. After deep intramuscular injection it forms a depot from which it is slowly absorbed and hydrolysed to benzylpenicillin. Benethamine penicillin is usually given with benzylpenicillin sodium and also sometimes procaine benzylpenicillin to produce both an immediate and a prolonged effect; overall, the effect lasts for 2 to 3 days.

Preparations

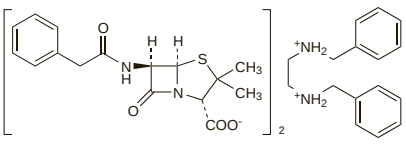
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Biclinocilline; ***Port.:*** Atralmicina.

Benzathine Benzylpenicillin *(BAN, rINN)*

Bensylpenicillinbensatin; Bensylpenicillinbenzatin; Bentsyylipenisilliinibentsatiini; Benzathin-benzylpenicilin; Benzathine benzylpénicilline; Benzathine Penicillin; Benzathini Benzylpenicillinum; Benzatin Penisilin; Benzatina bencilpenicilina; Benzethacil; Benzilpenicilinas benzatinas; Benzilpenicillina Benzatinica; Benzilpenicillin-benzantin; Benzylopenicylina benzatynowa; Benzylpenicillinum Benzanthinum; Benzylpenicillinum benzathinum; Penicillin G Benzathine; Penisilin G Benzatin; Penzaethinum G. *NN′*-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenylacetamido)penicillanate].

Бензатина Бензилпенициллин

$C_{16}H_{20}N_2(C_{16}H_{18}N_2O_4S)_2$ = 909.1.
CAS — 1538-09-6 (anhydrous benzathine benzylpenicillin); 5928-83-6 (benzathine benzylpenicillin monohydrate); 41372-02-5 (benzathine benzylpenicillin tetrahydrate).
ATC — J01CE08.
ATC Vet — QJ01CE08.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Int.* *Jpn* and *US* include the tetrahydrate.
Ph. Eur. 6.2 (Benzylpenicillin, Benzathine). It contains a variable quantity of water. A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide and in formamide. Store in airtight containers.
USP 31 (Penicillin G Benzathine). The tetrahydrate is a white, odourless, crystalline powder. Soluble 1 in 5000 of water and 1 in 65 of alcohol. pH in a solution prepared by dissolving 50 mg in 50 mL of dehydrated alcohol, and adding 50 mL of water is between 4.0 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Non-allergic (embolic-toxic) reactions similar to those associated with procaine benzylpenicillin, p.319, have been reported rarely with benzathine benzylpenicillin.

Benzathine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Interactions

As for Benzylpenicillin, p.214.

Pharmacokinetics

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see below).

Distribution into the CSF is reported to be poor.

Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.

Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gastrointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak concentrations are also produced less rapidly, but may persist for longer.

Plasma concentrations. Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks to ensure adequate plasma concentrations of benzylpenicillin. Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study[1] adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study,[2] in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900-mg dose of benzathine benzylpenicillin usually recommended might prolong the duration of protective plasma concentrations of benzylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against rheumatic fever.

1. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; **115:** 146–50.
2. Currie BJ, *et al.* Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrob Agents Chemother* 1994; **38:** 1203–4.

Pregnancy. The pharmacokinetics of benzathine benzylpenicillin appear to be altered in late pregnancy. Of 10 healthy pregnant women given benzathine benzylpenicillin 1.8 g intramuscularly before caesarean section, only 4 achieved adequate serum concentrations of benzylpenicillin (for syphilis, at least 18 nanograms/mL) for 7 days.[1]

1. Nathan L, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; **82**: 338–42.

Uses and Administration

Benzathine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p.214), to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations of benzylpenicillin produced, its use should be restricted to micro-organisms that are highly susceptible to benzylpenicillin. In acute infections, and when bacteraemia is present, the initial treatment should be with benzylpenicillin by injection.

Infections treated with benzathine benzylpenicillin include diphtheria (asymptomatic carriers), pharyngitis (*Streptococcus pyogenes; Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*)), and syphilis (including non-venereal treponematoses). It is also used for primary and secondary prophylaxis of rheumatic fever. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Benzathine benzylpenicillin is given by deep intramuscular injection, sometimes with procaine benzylpenicillin and benzylpenicillin itself. It has been given orally for mild infections, although phenoxymethylpenicillin is usually preferred. Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF. Infants up to 2 years of age may be given a single intramuscular dose of 37.5 mg/kg for the treatment of congenital syphilis, provided there is no evidence of infection in the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given; a dose of 450 mg may be used in children.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg; children under 30 kg may be given 225 to 675 mg. To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4 weeks to adults; a dose of 450 mg has been used for children under 30 kg.

Preparations

USP 31: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Benzathine Injectable Suspension; Penicillin G Benzathine Oral Suspension; Penicillin G Benzathine Tablets.

Proprietary Preparations (details are given in Part 3)

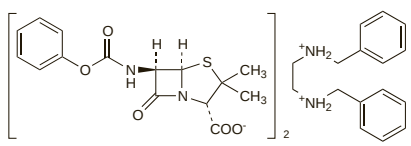
Arg.: Benzetacil; Galtamicina; Pen di Ben; Retarpen; ***Austral.:*** Bicillin L-A; ***Austria:*** Retarpen; ***Belg.:*** Penadur; ***Braz.:*** Bactopen; Benzatron; Benzetacil; Bepeben; Longacilin; Neo Benzil†; Pencil B; ***Cz.:*** Pendepon Compositum; Retarpen; ***Fr.:*** Extencilline; ***Ger.:*** Pendysin; ***Gr.:*** Penadur; ***Hung.:*** Retarpen†; ***India:*** Pencom; Penidure; ***Israel:*** Durabiotic; ***Ital.:*** Diaminocillina; Wycillina; ***Malaysia:*** Retarpen; ***Mex.:*** Benacilina; Bencelin; Benzafur; Benzanil Simple; Benzetacil; Ipenxin; Lentopenil; Unicil 6:3:3; Unicil L-A; ***Neth.:*** Penidural; ***NZ:*** Bicillin L-A; ***Philipp.:*** Penadur; Zalpen; ***Pol.:*** Debecylina; ***Port.:*** Lentocilin S; Penadur†; ***Rus.:*** Bicillin-1 (Бициллин-1); Extencilline (Экстенциллин); ***S.Afr.:*** Bicillin L-A; Penilente LA†; ***Singapore:*** Retarpen; ***Spain:*** Benzetacil; Cepacilina; ***Thai.:*** Penadur†; ***Turk.:*** Benzapen; Benzapen 6.3.3; Deposilin; Deposilin 6.3.3; Penadur; Penadur 6.3.3; ***USA:*** Bicillin L-A; Permapen; ***Venez.:*** Benzetacil L-A; Silcopen†.

Multi-ingredient: ***Austria:*** Retarpen compositum; ***Chile:*** Karbasalin†; ***Ger.:*** Retacillin compositum; Tardocillin; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Pecivax; Pendiben Compuesto; ***Neth.:*** Penidural D/F†; ***Port.:*** Lentocilin; Penadur 6.3.3†; ***Rus.:*** Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Benzetacil Compuesta; Cepacilina 633; Penilevel Retard; ***USA:*** Bicillin C-R; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Benzathine Phenoxymethylpenicillin

Benzatin Fenoksimetil Penisilin; Benzatina fenoximetilpenicilina; Penicillin V Benzathine *(USAN)*; Phenoxymethylpenicillini Dibenzylaethylendiaminum. *N,N′*-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenoxyacetamido)penicillanate].

$(C_{16}H_{18}N_2O_5S)_2,C_{16}H_{20}N_2$ = 941.1.
CAS — 5928-84-7 (anhydrous benzathine phenoxymethylpenicillin); 63690-57-3 (benzathine phenoxymethylpenicillin tetrahydrate).
ATC — J01CE10.
ATC Vet — QJ01CE10.



Pharmacopoeias. In *US.*
USP 31 (Penicillin V Benzathine). A practically white powder having a characteristic odour. Soluble 1 in 3200 of water, 1 in 330 of alcohol, 1 in 37 of acetone, 1 in 42 of chloroform, and 1 in 910 of ether. pH of a 3% suspension in water is between 4.0 and 6.5. Store in airtight containers.

Profile

Benzathine phenoxymethylpenicillin has actions and uses similar to those of phenoxymethylpenicillin (p.314) and is given orally in the treatment of susceptible mild to moderate infections. Doses are expressed in terms of phenoxymethylpenicillin.