Articaine Hydrochloride *(BANM, USAN, rINNM)*

40045; Articaïne, chlorhydrate d'; Articaini hydrochloridum; Artikaiinihydrokloridi; Artikain Hidroklorür; Artikain-hidroklorid; Artikain-hydrochlorid; Artikainhydroklorid; Artikaino hidrochloridas; Carticaine Hydrochloride; Carticaini Hydrochloridum; Hidrocloruro de articaína; Hoe-045; Karticainhydroklorid; Kartikaiinihydrokloridi; Kartikain Hidroklorür. Methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate hydrochloride.

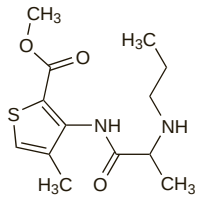
Артикаина Гидрохлорид

$C_{13}H_{20}N_2O_3S.HCl$ = 320.8.

CAS — 23964-58-1 (articaine); 23964-57-0 (articaine hydrochloride).

ATC — N01BB08.

ATC Vet — QN01BB08.



(articaine)

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

Ph. Eur. 6.2 (Articaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

Profile

Articaine hydrochloride is an amide local anaesthetic (p.1850). It has been used as a 1 or 2% solution with or without adrenaline for infiltration and regional anaesthesia. A 4% solution of articaine hydrochloride with adrenaline is used similarly in dentistry. A hyperbaric solution of articaine hydrochloride with glucose has been used for spinal block.

Porphyria. Articaine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Septanest; Ubistesin; Ultracain Dental; ***Belg.:*** Ubistesin†; ***Canad.:*** Astracaine†; ***Cz.:*** Septanest S; Supracain; Ubistesin; Ultracain D-S†; Ultracain†; ***Denm.:*** Septanest; Septocaine; Ubistesin; ***Fin.:*** Septocaine; Ubistesin; Ultracain D-Suprarenin; ***Fr.:*** Alphacaine; Predesic†; Ubistesin Adrenaliinee; ***Ger.:*** Ubistesin; Ultracain; Ultracain D-S; Ultracain hyperbar†; Ultracain Suprarenin; ***Hong Kong:*** Ubistesin; ***Hung.:*** Ubistesin; Ultracain D-S; ***Ital.:*** Alfacaina; Cartidont; Citocartin; Primacaine†; Sarticain; Septanest; Ubistesin; ***Neth.:*** Septanest; Ubistesin; Ultracain D-S; ***Norw.:*** Septocaine; ***NZ:*** Septanest; ***Port.:*** Alphacaine; Artinibsa; Artinostrum; Meganest; Septanest; Ubistesin; ***Rus.:*** Ultracain (Ультракаин); ***Spain:*** Articaina C/E; Meganest; Ultracain; ***Switz.:*** Alphacaine; Rudocaine; Septanest; Ubistesin; Ultracaine D-S; ***Turk.:*** Ultracain; ***UK:*** Septanest; ***USA:*** Septocaine.

Benzocaine *(BAN, rINN)*

Anaesthesinum; Anestezin; Anesthamine; Bensokain; Bentsokaiini; Benzocaína; Benzocaïne; Benzocainum; Benzokain; Benzokaina; Benzokainas; Ethoform; Éthoforme; Ethyl Aminobenzoate; Ethylis Aminobenzoas. Ethyl 4-aminobenzoate.

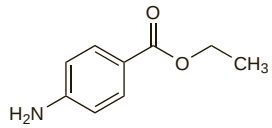
Бензокаин

$C_9H_{11}NO_2$ = 165.2.

CAS — 94-09-7.

ATC — C05AD03; D04AB04; N01BA05; R02AD01.

ATC Vet — QC05AD03; QD04AB04; QN01AX92; QN01BA05; QR02AD01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of benzocaine:
Coco snow.

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

Ph. Eur. 6.2 (Benzocaine). Colourless crystals or a white or almost white, crystalline powder. M.p. 89° to 92°. Very slightly soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Benzocaine). Small, white crystals or a white odourless crystalline powder. M.p. 88° to 92°. Soluble 1 in 2500 of water, 1 in 5 of alcohol, 1 in 2 of chloroform, 1 in 4 of ether, and 1 in 30 to 50 of almond oil or olive oil; dissolves in dilute acids.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Abuse. Benzocaine has been used as an adulterant or 'cutting' agent in the preparation of cocaine for illicit use and adverse effects such as methaemoglobinaemia have been seen after cocaine overdosage as a result of the benzocaine content.[1]

1. McKinney CD, *et al.* Benzocaine-adultered street cocaine in association with methemoglobinemia. *Clin Chem* 1992; **38:** 596–7.

Hypersensitivity. The incidence of positive reactions in patients patch tested with benzocaine has ranged from 3.3 to 5.9%.[1,2] Patch testing with benzocaine has been recommended by The International Contact Dermatitis Research Group as an indicator of contact hypersensitivity to local anaesthetics. However, it was found that of 40 patients who had had positive reactions to benzocaine with tetracaine and cinchocaine, 21 were not allergic to benzocaine alone.[3]

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.
2. Bandmann H-J, *et al.* Dermatitis from applied medicaments. *Arch Dermatol* 1972; **106:** 335–7.
3. Beck MH, Holden A. Benzocaine—an unsatisfactory indicator of topical local anaesthetic sensitization for the UK. *Br J Dermatol* 1988; **118:** 91–4.

Precautions

As for Local Anaesthetics in general, p.1851.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

See under Local Anaesthetics, p.1852.

Uses and Administration

Benzocaine, a para-aminobenzoic acid ester, is a local anaesthetic used for surface anaesthesia (p.1853); it has low potency and low systemic toxicity. It is used, often with other drugs such as analgesics, antiseptics, antibacterials, antifungals, and antipruritics, for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, haemorrhoids, anal pruritus, and ear pain.

Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat. Gels, pastes, solutions, and sprays containing benzocaine in concentrations of up to 20% have been used for surface anaesthesia of the mouth and throat.

Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations up to 20% for topical analgesia and anaesthesia.

Benzocaine has also been used as the hydrochloride.

Obesity. It has been reported[1] that despite the inclusion of benzocaine in some over-the-counter appetite suppressants there is no good evidence of its value in obesity (p.2149).

1. Anonymous. A nasal decongestant and a local anesthetic for weight control? *Med Lett Drugs Ther* 1979; **21:** 65–6.

Preparations

USP 31: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Benzocaine and Menthol Topical Aerosol; Benzocaine Cream; Benzocaine Gel; Benzocaine Lozenges; Benzocaine Ointment; Benzocaine Otic Solution; Benzocaine Topical Aerosol; Benzocaine Topical Solution; Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cerax; Lanacaina†; Lodoc; ***Austral.:*** Applicaine; ***Austria:*** Anaestherit; ***Braz.:*** Solarcaine; ***Canad.:*** Anbesol; Anbesol Baby; Anbesol Extra Strength; Baby Orajel; Detane†; Maintain; ManDelay; Orajel; Outgro; Zilactin Baby; Zilactin Tooth & Gum Pain Reliever; Zilactin Toothache Swab; Zilactin-B; ***Chile:*** Anbesol; Baby Orajel†; BBdent Gel Topico; Dentispray; Foille; Kalmafta; Orajel†; ***Cz.:*** Babydent; ***Ger.:*** Anaesthesin; Anaesthesin N; Flavamed Halstabletten†; Kontakto Derm†; Labocane; Subcutin N; Zahnerol N†; ***Hung.:*** Babydent; ***Israel:*** Anadent; Baby Gel; Lanacane; Maintain; ***Mex.:*** Auralyt; Gomas Garde B; Graneodin B; ***NZ:*** Solarcaine; ***Pol.:*** Baby Orajel; Orajel; ***Port.:*** Dentispray; Topigel; ***Rus.:*** Relief Advance (Релиф Адванс); ***S.Afr.:*** Kiddigum; ***Spain:*** Dentispray; Gartricin†; Hurricaine; Lanacane; Nani Pre Dental; ***UK:*** AAA; Burneze; Lanacane; Orajel; Ultra Chloraseptic; Ultracare; ***USA:*** Americaine Anesthetic†; Americaine Otic†; Americaine†; Baby Anbesol; Baby Orajel; Benz-O-Sthetic; Benzodent; Chiger-Tox; Dent's Extra Strength Toothache Gum; Dent's Maximum Strength Toothache Drops; Dent-O-Kain; Dermoplast; Detane; Hurricaine; Lanacane; Medicone; Mycinettes; Numzident†; Orabase Baby; Orabase Gel; Orabase-B; Orajel; OraMagic Plus; Otocain; SensoGARD; Trocaine; Zilactin-B Medicated.

Multi-ingredient: ***Arg.:*** Adermicina; Adermicina A; Algiodent; Anginotrat; Apracur Bucofaringeo†; Arnecrem†; Aseptobron Caramelos; Aseptobron N; Bagociletas; Balsamina; Bucoangin N; Bucotricin; Caext; Callicida; Caramelos Antibioticos; Caramelos Antibioticos Lefmar; Caramelos Oriental; Carnot Colutorio; Cartiflex; Collubiazol; Coltix†; Cristalomicina; Dermo Vagisil Crema; Dermosan; Detebencil; Dotrin; Esculeol P; Esmedent con Fluor; Fanaletas; Filotricin A; Flebotropin†; Fonergine; Gargaletas; Graneodin; Graneodin N; Hexa-Defital; Iodotiazol†; Leroid†; Lyndan; Muco-Anestyl†; Mucobase; Muelita; Nene Dent; Neo Coltirot; No-Tos Pocket; Oralsone C; Otocalmia; Otoseptil; Parencias†; Pastillas Lorbi; Pastillas Medex; Pruripelen†; Pulmosan Caramelos; Razagleda Plus†; Salicrem; Sapucai†; Suavisan N; Suavisan†; Sulfanoral T; Tavinex; ***Austral.:*** Animine; Auralgan; Ayrton's Chilblain; Cepacaine; Cepacol Anaesthetic; Cepacol Cough & Sore Throat; Cornkil†; Le Trim-BM†; Nyal Toothache Drops; Rectinol; ***Austria:*** Dequalinetten; Dorithricin; Herposicc; Sulgan 99; Tyrothricin comp; Tyrothricin compositum; ***Belg.:*** Transvane; ***Braz.:*** Albicon; Amidalin†; Amigdagen; Amigdamicin†; Andolba; Anginotricin; Bromil; Cepacaina; Cetildrops†; Claudemor; Dentalivio†; Dequadin; Fenotricin†; Gargotan†; Gingilone; Larintil†; Malvatricin Pastilhas; Malvona†; Mentozil†; Mirorroidin†; Neopiridin; Otovix†; Passilin†; Predmicin; Sanilin; Senol†; Silencium; Traumac; ***Canad.:*** Anbesol Maximum Strength; Antibiotic Cold Sore Ointment; Appedrine†; Auralgan; Bionet; Boil Ease†; Cepacol Extra Strength; Chloraseptic Lozenges; Dexatrim†; Endospray†; Kank-A; Lanacane Medicated Cream; Onrectal; Orajel Mouth Sore Medicine; Orajel Ultra Mouth Sore; Osmopak-Plus; Oxipor; Rectogel; Rectogel HC; Solarcaine; Sore Throat Lozenges; Tanac; Thermo-Gel; Throat Lozenges; Thunas Pile†; Vagisil; ***Chile:*** Aucusik; Cariamyl; Kank-Eze; Konirub; Lerfimin; Medikem†; Orajel Compuesto†; Otandrol; Solarcaine Spray Aerosol; ***Cz.:*** Dr Rentschler Halstabletten†; Herbadent; Hexoral; Hexoraletten N; ***Denm.:*** Dolodent; Hexokain; ***Fin.:*** Bafucin; Toncils; ***Fr.:*** Nestosyl; Sedorrhoide; ***Ger.:*** Anaesthesin-Rivanol; Combustin Heilsalbe; Dolo-Dobendan; Dorithricin Original; Eulatin NN; Frubizin Forte†; Gelum†; Hexoraletten N; Inspirol Halsschmerztabletten†; Nordapanin N†; Nordathricin N†; Salistoperm†; Stipo†; Trachiform†; Tyrosolvetten†; ***Gr.:*** Myalgesic†; ***Hong Kong:*** Borraginol-N; Pharynx; Setronges†; Tyricine; Tyrocaine; Tyrothricin Co; ***Hung.:*** Almagel A; Dorithricin; ***India:*** Chloromycetin Ear Drops; Clearwax Healex; Nit-N-Mite†; Paraxin Ear†; Perfocyn; Proctosedyl; Scaboma; Tytin; Waxolve; ***Indon.:*** Benzomid; Borraginol-N; Borraginol-S; FG Ointment; Otolin; ***Irl.:*** Dequacaine; Merocaine; Tyrozets; ***Israel:*** Anadent†; Dentin; Gingisan; Hemo; Kalgaron; Kank-A; Noxacorn; Otomycin; Proctozorin-N; Pronestin; Rafathricin with Benzocaine; Rectozorin; ***Ital.:*** Antiscabbia Candioli al DDT Terapeutico; Antiscabbia CM; Boma; Dentosedina; Fialetta Odontalgica Dr Knapp; Foille Scottature; Foille Sole; Golamixin; Labocaina; Pinselina Knapp; Prepacort H; Preparazione Antiemorroidaria†; Proctidol; Proctosedyl; Proctosoll; Sedalen Cort†; Sedilene Procto†; ***Malaysia:*** Cetylpyridinium B; Horf; Pharynx; Setronges†; ***Mex.:*** Cepacaina; Cloran Otico; Graneodin D Mentol; Ofodex; Otifar; Otolone†; Soldrin; Sufrexal P; Trociletas B; ***NZ:*** Auralgan; Cepacaine; Cepacol Anaesthetic; Cepacol Cough Discs; Lanacane; Solarcaine; Toothache Drops†; ***Philipp.:*** Auralgan; United Home Burn Ointment; ***Pol.:*** Dentosept A; Dermopur; Hemorol; Icy Rub; Puder Plynny; Puder Plynny z Anestezyna; Pudroderm; Pudrospan; Rectosec; Sanofil; Sapoven AT; Savarix; Septolete Plus; Variderm; ***Port.:*** Afonina; Anginova; Claudemor†; Dek; Dropcina; Halitol†; Hibitane Menta†; Hibitane†; Medifon; Mentocaina R; Otoceril; Solpic†; Tantum Verde; ***Rus.:*** Almagel A (Алмагель А); Anaesthesol (Анестезол); Heparin Ointment (Гепариновая Мазь); Nigepan (Нигепан); Septolete Plus (Септолете Плюс); ***S.Afr.:*** AAA†; Auralyt; Aurasept; Aurone Forte; Benzet†; Calasthetic; Cepacaine; Cepacol Cough Discs; Cetoxol; Covancaine; Covotop; Endcol Lozenges; Histamed; Medi-Kain†; Medi-Keel A; Orochlor; Otised; Oto-Phen Forte; Oxipor VHC; Prodol; Trochain; Viodor; ***Singapore:*** Dorithricin; Pharynx; ***Spain:*** Angileptol; Antihemorroidal; Bucodrin; Bucometasana; Bucospray; Callicida Rojo; Callivoro Marthand; Callix; Caltoson Balsamico; Cicatral; Cremsol; Dentikrisos; Diformiltricina; Drill; Edifaringen; Faringenilo; Faringesic; Gargaril; Garydol; Gradin Del D Andreu†; Grietalgen; Grietalgen Hidrocort†; Hemoal; Hemodren Compuesto†; Hibitane; Mastiol; Miozets; Nasopomada; Neo Analsona; Oto Difusor†; Oto Vitna†; Otocerum; Otonina†; Otosedol Biotico; Pastillas Koki Ment Tiro; Phonal; Sedofarin; Topicaina†; Tos Mai; Vicks Formula 44†; ***Swed.:*** Bafucin; ***Switz.:*** Benzocaine PD; Neocones; ***Thai.:*** Auralgan†; Doproct; Iwazin; Sigatricin; Trocacin; Troneo†; ***Turk.:*** Emedur; Kataljin; Kortos; Ma-Ka-Ta; ***UK:*** Anthisan Plus; Dequacaine; Intralgin†; Merocaine; Rinstead; Solarcaine; Tyrozets; Wasp-Eze; ***USA:*** Aerocaine†; Allergen; Americaine First Aid†; Anbesol; Anbesol Cold Sore Therapy; Auralgan; Auroguard Otic; Auroto†; Babee; Bicozene; Boil Ease; Boyol Salve; Calamycin; Cepacol Anesthetic; Cepacol Maximum Strength Sore Throat; Cepacol Ultra Sore Throat Plus Cough; Cetacaine; Chiggerex; Chloraseptic Sore Throat; Cough-X; Cy-Gesic; Cylex; Dendracin Neurodendtraxcin; Dentapaine; Dermacoat; Dermasept Antifungal; Dermoplast Antibacterial; Double-Action Toothache Kit; Foille; Fungi-Nail; Hem-Prep; Kank-A; Legatrin Rub; Lipmagik; Maximum Strength Anbesol; Medicone Derma†; Numzit†; Orabase Lip; Orajel Mouth Aid; Orajel PM; Orasept; Orasol; Otocalm†; Pazo; Rectagene Medicated Rectal Balm; Rid-a-Pain; Solarcaine; Soothaderm; Sting-Eze; Sting-Kill; Tanac; Tanac Dual Core; Therevac Plus; Tigan†; Toothache Gel; Triban†; Tympagesic†; Unguentine Maximum Strength; Vagi-Gard Medicated Cream; Vagisil; Z-Xtra; ***Venez.:*** Claudemor†; Otan; Otofrin†.

Bupivacaine Hydrochloride

(BANM, USAN, rINNM)

AH-2250; Bupivacaïne, chlorhydrate de; Bupivacaini hydrochloridum; Bupivacaini Hydrochloridum Monohydricum; Bupivakaiinihydrokloridi; Bupivakain Hidroklorür; Bupivakain-hidroklorid; Bupivakain-hydrochlorid monohydrát; Bupivakainhydroklorid; Bupivakaino hidrochloridas; Bupiwakainy chlorowodorek; Hidrocloruro de bupivacaína; LAC-43; Win-11318. (±)-(1-Butyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride monohydrate.

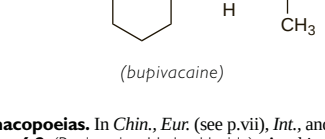
Бупивакаина Гидрохлорид

$C_{18}H_{28}N_2O.HCl.H_2O$ = 342.9.

CAS — 2180-92-9 (bupivacaine); 18010-40-7 (anhydrous bupivacaine hydrochloride); 14252-80-3 (bupivacaine hydrochloride monohydrate).

ATC — N01BB01.

ATC Vet — QN01BB01.



(bupivacaine)

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

Ph. Eur. 6.2 (Bupivacaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Bupivacaine Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in acetone and in chloroform. A 1% solution in water has a pH of 4.5 to 6.0.

Stability of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

For reference to the stability of admixtures of bupivacaine and fentanyl in solution, with or without adrenaline, see under Fentanyl, p.56.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Bupivacaine appears to be more cardiotoxic than other local anaesthetics. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts.

◊ For reference to the toxic threshold for bupivacaine plasma concentrations, see Absorption under Pharmacokinetics, below.

Effects on the cardiovascular system. Bupivacaine[1,2] and etidocaine[2] appear to be more cardiotoxic than most other commonly used local anaesthetics and marked cardiovascular depression may occur at plasma concentrations only slightly above those for CNS toxicity.[2] Fatalities have occurred. Simultaneous seizures and cardiovascular collapse may develop rapidly on inadvertent intravascular injection and even prompt oxygenation and blood pressure support might not prevent cardiac arrest.[2] Ventricular fibrillation which is very resistant to normal methods of defibrillation may develop. Since lidocaine and the other local anaesthetics have additive effects on the CNS bretylium may be preferable to lidocaine for the treatment of induced arrhythmias.[1] Seizures and life-threatening ventricular fibrillation have also been reported after systemic absorption of bupivacaine solutions in an adolescent patient undergoing wound debridement.[3] Fatal cardiotoxicity has occurred after the use of bupivacaine in intravenous regional anaesthesia, possibly due to leakage past the tourniquet, and the use of bupivacaine in this technique should be avoided.[1] Fatalities have also been associated with the use of 0.75% solutions for epidural anaesthesia in obstetric patients and this strength is no longer recommended for obstetric anaesthesia. See also Labour Pain under Uses and Administration, below.

1. Anonymous. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; **ii:** 1192–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51:** 285–7.
3. Yan AC, Newman RD. Bupivacaine-induced seizures and ventricular fibrillation in a 13-year-old girl undergoing wound debridement. *Pediatr Emerg Care* 1998; **14:** 354–5.

Effects on the eyes. Bilateral retinal haemorrhages developed in a 47-year-old woman[1] after receiving a caudal block with bupivacaine 0.5%. The haemorrhages cleared and her usual vision returned by 3 months.

1. Ling C, *et al.* Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993; **77:** 316–17.

Prolonged block. Use of bupivacaine in regional anaesthesia may result in prolonged block.[1,2]

1. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. *Br J Anaesth* 1975; **47:** 520–2.
2. Brockway MS, *et al.* Prolonged brachial plexus block with 0.42% bupivacaine. *Br J Anaesth* 1989; **63:** 604–5.

Precautions

As for Local Anaesthetics in general, p.1851.

Bupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Renal impairment. Spinal block was more rapid in onset and of shorter duration in patients with chronic renal failure given 3 mL of bupivacaine 0.75% than in control patients.[1]

1. Orko R, *et al.* Subarachnoid anaesthesia with 0.75% bupivacaine in patients with chronic renal failure. *Br J Anaesth* 1986; **58:** 605–9.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Antiarrhythmics. There is an increased risk of myocardial depression when bupivacaine and antiarrhythmics are given together.

Beta blockers. *Propranolol* reduced the clearance of bupivacaine by 35% in 6 healthy subjects.[1] There is a risk of increased bupivacaine toxicity if these drugs are used together.

1. Bowdle TA, *et al.* Propranolol reduces bupivacaine clearance. *Anesthesiology* 1987; **66:** 36–8.

Calcium-channel blockers. There is a theoretical risk that the adverse effects of bupivacaine on the heart might be enhanced in patients taking calcium-channel blockers, but evidence of a clinical problem is lacking.

Histamine H_2-antagonists. Studies of the effect of H_2-antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While a group of workers[1] found that pretreatment with *cimetidine* decreased the clearance of bupivacaine, others have failed to find any significant pharmacokinetic effects.[2,3] Similarly, pretreatment with *ranitidine* has either increased plasma concentrations of bupivacaine[4] or had no significant effect.[3]

1. Noble DW, *et al.* Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* 1987; **59:** 735–7.
2. Pihlajamäki KK. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* 1988; **26:** 403–6.
3. Flynn RJ, *et al.* Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* 1989; **62:** 87–91.
4. Wilson CM. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* 1986; **58:** 1330P–1331P.

Local anaesthetics. For reference to the effect of bupivacaine on the protein binding of *lidocaine* and *mepivacaine*, see p.1864 and p.1866, respectively.

Pharmacokinetics

Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine mainly as metabolites with only 5 to 6% as unchanged drug.

Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

See also under Local Anaesthetics, p.1852.

Absorption. The toxic threshold for bupivacaine plasma concentrations is considered by some[1] to lie in the range of 2 to 4 micrograms/mL and in the UK the maximum single recommended dose for anhydrous bupivacaine hydrochloride is 150 mg (equivalent to about 2 mg/kg). Giving bupivacaine for *regional anaesthesia* of the head and neck in a mean total dose of 3.4 mg/kg has produced mean peak plasma concentrations of 3.56 micrograms/mL (with adrenaline) and 4.95 micrograms/mL (without adrenaline), without producing toxicity.[2] Similarly, *intrapleural* bupivacaine 0.5% in a dose of 2.5 mg/kg has produced mean peak plasma concentrations of 2.57 and 3.22 micrograms/mL (with or without adrenaline, respectively) without producing toxicity.[3] A further study[4] in which a 72-hour interpleural infusion of bupivacaine hydrochloride with adrenaline was given to cholecystectomy patients showed appreciable interpatient variability in steady-state plasma drug concentrations (range 1.3 to 3.2 micrograms/mL; mean 2.1 micrograms/mL); no patient suffered any adverse effects. Bilateral *intercostal* nerve blocks using bupivacaine 2 mg/kg have also produced concentrations within the presumed toxic range without adverse effects but the use of adrenaline with this block did not reliably reduce peak plasma-bupivacaine concentrations.[5]

Stellate ganglion block with bupivacaine 0.25% has produced a mean peak plasma concentration of 0.34 and 0.47 micrograms/mL after doses of 10 or 20 mL, respectively.[6] Giving bupivacaine 0.5% in a dose of 3 mg/kg with or without adrenaline for *sciatic* and *femoral nerve block* produced mean peak plasma concentrations below 0.8 micrograms/mL.[7]

Intra-articular bupivacaine is rapidly absorbed from the synovial membrane of the knee during arthroscopy but plasma concentrations did not exceed 0.35 micrograms/mL after controlled pressure-irrigation with isotonic solutions containing up to 200 mg.[8] Although a group of workers found that the maximum plasma concentrations of bupivacaine after intra-articular injection of 30 mL of a 0.5% solution for arthroscopy was 0.875 micrograms/mL they suggested that adrenaline should probably be added to minimise absorption.[9]

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; **56:** 485–92.
3. Gin T, *et al.* Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. *Br J Anaesth* 1990; **64:** 662–6.
4. Kastrissios H, *et al.* The disposition of bupivacaine following a 72h interpleural infusion in cholecystectomy patients. *Br J Clin Pharmacol* 1991; **32:** 251–4.
5. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* 1990; **64:** 436–41.
6. Hardy PAJ, Williams NE. Plasma concentrations of bupivacaine after stellate ganglion block using two volumes of 0.25% bupivacaine plain solution. *Br J Anaesth* 1990; **65:** 243–4.
7. Misra U, *et al.* Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; **66:** 310–13.
8. Debruyne D, *et al.* Monitoring serum bupivacaïne levels during arthroscopy. *Eur J Clin Pharmacol* 1985; **27:** 733–5.
9. Butterworth JF, *et al.* Effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection of bupivacaine for knee arthroscopy. *Br J Anaesth* 1990; **65:** 537–9.

SURFACE ANAESTHESIA. Studies of the absorption of bupivacaine after surface application.

1. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.

Pregnancy. Bupivacaine crosses the placenta to a lesser degree than lidocaine or mepivacaine following maternal injection. Values of 0.2 to 0.4 have been reported[1,2] for the ratio of fetal to maternal concentrations for bupivacaine compared with values of 0.5 to 0.7 quoted[2,3] for lidocaine and mepivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the fetal circulation[2] (see also under Protein Binding, below). Addition of adrenaline to the injection does not appear to affect the placental transfer rate of bupivacaine.[4] Measurement of a beta-phase half-life of 25 hours in the neonate compared with 1.25 hours in mothers suggests that the neonate is less able to metabolise bupivacaine.[5]

1. Denson DD, *et al.* Serum bupivacaine concentrations in term parturients following continuous epidural analgesia for labor and delivery. *Ther Drug Monit* 1984; **6:** 393–8.
2. Blogg CE, Simpson BR. Obstetric analgesia and the newborn baby. *Lancet* 1974; **i:** 1283.
3. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
4. Reynolds F, *et al.* Effect of time and adrenaline on the feto-maternal distribution of bupivacaine. *Br J Anaesth* 1989; **62:** 509–14.
5. Caldwell J, *et al.* Pharmacokinetics of bupivacaine administered epidurally during childbirth. *Br J Clin Pharmacol* 1976; **3:** 956P–957P.

Protein binding. The two major binding proteins for bupivacaine in the blood are α_1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α_1-acid glycoprotein for bupivacaine but has no effect on albumin affinity.[1] Binding of bupivacaine is reduced during pregnancy but it is considered that the increase in free bupivacaine concentrations is unlikely to cause a clinically significant increase in the risk of CNS or cardiovascular toxicity.[2]

As fetal plasma contains little α_1-acid glycoprotein the binding capacity for bupivacaine is reduced and this may contribute to the difference between maternal and fetal plasma concentration at delivery[3] (see also under Pregnancy, above).

Ageing, uncomplicated by disease, does not affect the protein binding of bupivacaine.[4]

1. Denson D, *et al.* Alpha -acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 1984; **35:** 409–15.
2. Denson DD, *et al.* Bupivacaine protein binding in the term parturient: effects of lactic acidosis. *Clin Pharmacol Ther* 1984; **35:** 702–9.
3. Petersen MC, *et al.* Relationship between the transplacental gradients of bupivacaine and α -acid glycoprotein. *Br J Clin Pharmacol* 1981; **12:** 859–62.
4. Veering BT, *et al.* Age does not influence the serum protein binding of bupivacaine. *Br J Clin Pharmacol* 1991; **32:** 501–3.

Uses and Administration

Bupivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It has a slow onset and a long duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor, and absorption into the circulation from the site of injection is reduced. Slow accumulation occurs with repeated doses. It is used mainly for infiltration anaesthesia and regional nerve blocks, particularly epidural block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural block in obstetrics. (Local anaesthetic techniques are discussed on p.1853.)

Bupivacaine is a racemic mixture but the *S*(−)-isomer levobupivacaine (see p.1862) is also used. The carbonated solution of bupivacaine is also available for injection in some countries (see p.1852).

In recommended doses bupivacaine produces complete sensory blockade but the concentration of bupivacaine solution used affects the extent of motor blockade achieved. A 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce motor block and some muscle relaxation, and complete motor block and muscle relaxation can be achieved with a 0.75% solution.

The dosage of bupivacaine used depends on the site of injection and the procedure used, as well as the status of the patient. Bupivacaine is given as the hydrochloride monohydrate salt although doses are expressed in

terms of the anhydrous hydrochloride; bupivacaine hydrochloride monohydrate 10.55 mg is equivalent to about 10 mg anhydrous bupivacaine hydrochloride. In the UK the suggested general **maximum single dose** of bupivacaine hydrochloride is 150 mg with or without adrenaline followed if necessary by doses of up to 50 mg every 2 hours. In the USA the recommended maximum single dose is 175 mg of the plain preparation or 225 mg when given with adrenaline; doses may be repeated at intervals of not less than 3 hours but the total daily dose should not exceed 400 mg. The dose should be reduced in the elderly, in children, in debilitated patients, and in cardiac or hepatic disease.

A test dose of bupivacaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Subsequent doses should be given in small increments.

Solutions with or without adrenaline may be used for most **local anaesthetic techniques** and procedures apart from dental infiltration, when adrenaline is added to the solution (see below).

- For *infiltration anaesthesia* bupivacaine hydrochloride is typically used as a 0.25% solution in doses up to the recommended maximum (see above). When a longer duration of anaesthesia is required, as in dental or surgical procedures of the maxillary and mandibular area, a 0.5% solution with adrenaline 1 in 200 000 has been used but a total dose of 90 mg (18 mL) should not be exceeded over a single dental sitting.
- For *peripheral nerve block* the usual dose is 12.5 mg (5 mL) as a 0.25% solution or 25 mg (5 mL) as a 0.5% solution, although doses up to the recommended maximum single dose (see above) may also be given. A 0.75% solution has been used for *retrobulbar block* in ophthalmic surgery in a dose of 15 to 30 mg (2 to 4 mL).
- For *sympathetic nerve block* 50 to 125 mg (20 to 50 mL) as a 0.25% solution is recommended.
- For *lumbar epidural block* in surgery a 0.25% solution of bupivacaine hydrochloride may be used in a dose of 25 to 50 mg (10 to 20 mL) or as a 0.5% solution in a dose of 50 to 100 mg (10 to 20 mL). A 0.75% solution is also used for induction of lumbar epidural block in non-obstetric surgery in a single dose of 75 to 150 mg (10 to 20 mL). For *caudal block* in surgery 37.5 to 75 mg (15 to 30 mL) as a 0.25% solution or 75 to 150 mg (15 to 30 mL) as a 0.5% solution may be used. In the management of **acute pain** bupivacaine may be given as an epidural bolus or by continuous infusion. For analgesia during *labour*, doses of 15 to 30 mg (6 to 12 mL) as a 0.25% solution or 30 to 60 mg (6 to 12 mL) as a 0.5% solution have been recommended as a bolus for lumbar block. Alternatively, when given as an infusion, a dose of 10 to 15 mg (10 to 15 mL) per hour as a 0.1% solution or 10 to 15 mg (8 to 12 mL) per hour as a 0.125% solution has been recommended for lumbar block. Bupivacaine may also be given as a bolus caudal injection for labour pain; doses of 25 to 50 mg (10 to 20 mL) as a 0.25% solution or 50 to 100 mg (10 to 20 mL) as a 0.5% solution are recommended. For *postoperative pain* bupivacaine may be given as an epidural infusion in doses of 4 to 15 mg (4 to 15 mL) per hour as a 0.1% solution or 5 to 15 mg (4 to 12 mL) per hour as a 0.125% solution.
- Hyperbaric solutions of bupivacaine hydrochloride without adrenaline may be used for *spinal block*. Preparations containing 0.5% are available and are given in doses of 10 to 20 mg (2 to 4 mL).

Action. Addition of potassium chloride 0.2 mmol to 40 mL of bupivacaine 0.25% solution resulted in a more rapid onset of sensory loss than the same dose of plain bupivacaine in patients undergoing brachial plexus block for forearm or hand surgery.[1]

Hyaluronidase did not increase the speed of onset of brachial plexus block produced by bupivacaine 0.5%, with or without adrenaline, but did reduce the duration of anaesthesia.[2]

Bupivacaine encapsulated in liposomes can prolong postsurgical analgesic action without motor block.[3,4]

For a comparison of the vasoactivity of bupivacaine and some other local anaesthetics, see p.1852.

1. Parris MR, Chambers WA. Effects of the addition of potassium to prilocaine or bupivacaine: studies on brachial plexus blockade. *Br J Anaesth* 1986; **58:** 297–300.
2. Keeler JF, *et al.* Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992; **68:** 68–71.
3. Boogaerts S, *et al.* Epidural administration of liposomal bupivacaine for the management of postsurgical pain. *Br J Anaesth* 1993; **70:** (suppl 1): 104.
4. Boogaerts JG, *et al.* Pharmacokinetic-pharmacodynamic specific behaviour of liposome-associated bupivacaine in humans. *Br J Anaesth* 1995; **74** (suppl 1): 74.

Administration in children. Bupivacaine 0.25% injected intra-operatively up to a maximum dose of 1.5 mg/kg with adrenaline has been used in infants for the control of postoperative pain due to pyloromyotomy and appears to attenuate some of the cardiac and respiratory effects associated with the use of general anaesthesia alone.[1] Doses of 2.5 mg of bupivacaine for each year of age, as a 0.5% solution, have been used for ilio-inguinal nerve block in children undergoing herniotomy.[2] A study[3] in infants undergoing abdominal surgery found that an epidural infusion of bupivacaine produced comparable analgesia to an intravenous infusion of morphine. It was considered that bupivacaine might be preferable to morphine in neonates and young infants who are particularly prone to respiratory depression, but older children might require additional sedation or analgesia to prevent postoperative restlessness.

1. McNicol LR, *et al.* Peroperative bupivacaine for pyloromyotomy pain. *Lancet* 1990; **335:** 54–5.
2. Smith BAC, Jones SEF. Analgesia after herniotomy in a paediatric day unit. *BMJ* 1982; **285:** 1466.
3. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70:** 10–16.

Labour pain. For a discussion of the management of labour pain, including mention of the use of local anaesthetics, see p.7.

Early experience in nearly 1000 patients suggested that 8 mL of a 0.5% solution of bupivacaine with adrenaline was the optimum dose for epidural block during labour;[1] pain relief lasted for about 2 hours. Decreasing the concentration of the final dose to 0.25% reduced the persistence of sensory and motor nerve block after delivery. Others[2] found that bupivacaine 0.375% was the most suitable concentration for epidural analgesia when using a regimen of regular 'top-up' doses of 0.5 mg/kg about every 90 minutes. However, the use of low doses of bupivacaine 0.25% for epidural analgesia in primiparous women was associated with a lower incidence of forceps delivery and oxytocin augmentation.[3] Although an even lower concentration of bupivacaine (0.0625%) used with sufentanil[4] produced analgesia similar to that with 0.125% bupivacaine used alone, the duration of the second stage of labour and the incidence of instrumental and surgical delivery were not reduced. Similar results were obtained using bupivacaine 0.0625% with diamorphine 0.005%; in addition pruritus and drowsiness produced by diamorphine were considered to be troublesome in many patients.[5] However, a large UK study[6,7] compared a traditional epidural regimen using 10 mL boluses of bupivacaine 0.25% given up to every hour, with two lower-dose regimens using bupivacaine 0.1% with fentanyl 2 micrograms/mL, and found the lower dose techniques were at least as effective and were associated with a lower incidence of instrumental delivery.

Combined spinal-epidural blocks, in which an initial intrathecal injection of bupivacaine or bupivacaine with an opioid is given before starting the epidural, are also used,[6-9] and have been found to give excellent results,[7] although they may have no advantages over a low-dose epidural technique.[10]

Intrathecal injections containing bupivacaine have also been given alone[11,12] for the management of labour pain but the use of this route alone is usually associated with anaesthesia and management of postoperative pain in caesarean section. Bupivacaine has also been tried with lidocaine for epidural anaesthesia in caesarean section in order to reduce the dose of bupivacaine and minimise cardiotoxicity.[13]

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *Br J Anaesth* 1972; **44:** 66–74.
2. Purdy G, *et al.* Continuous extradural analgesia in labour: comparison between "on demand" and regular "top-up" injections. *Br J Anaesth* 1987; **59:** 319–24.
3. Turner MJ, *et al.* Primiparous women using epidural analgesia. *BMJ* 1990; **300:** 123.
4. Auroy Y, Benhamou D. Extradural analgesia for labour: 0.125% bupivacaine vs 0.0625% bupivacaine with 0.2 micrograms mL sufentanil. *Br J Anaesth* 1995; **74** (suppl 1): 105–6.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; **358:** 19–23.
7. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Randomized controlled trial comparing traditional with two "mobile" epidural techniques: anesthetic and analgesic efficacy. *Anesthesiology* 2002; **97:** 1567–75.
8. Stacey RGW, *et al.* Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71:** 499–502.
9. Collis RE, *et al.* Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345:** 1413–16.
10. Simmons SW, *et al.* Combined spinal-epidural versus epidural analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/02/08).
11. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
12. McHale S, *et al.* Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *Br J Anaesth* 1992; **69:** 634–6.
13. Howell P, *et al.* Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *Br J Anaesth* 1990; **65:** 648–53.

Preparations

BP 2008: Bupivacaine and Adrenaline Injection; Bupivacaine Injection; ***USP 31:*** Bupivacaine Hydrochloride in Dextrose Injection; Bupivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Bupicaina; Bupigobbi; Bupinex; Caina G; Duracaine; ***Austral.:*** Marcain; ***Austria:*** Bucain; Carbostesin; Dolanaest; ***Belg.:*** Marcaine; ***Braz.:*** Bupiabbott; Bupiabbott Plus; Marcaina; Neocaina; ***Canad.:*** Marcaine; Sensorcaine; ***Chile:*** Duracaine†; ***Cz.:*** Marcaine; ***Denm.:*** Marcain; ***Fin.:*** Bicain; Marcain; ***Fr.:*** Marcaine†; ***Ger.:*** Bucain; Carbostesin; Dolanaest; ***Gr.:*** Marcaine; ***Hong Kong:*** Marcain; ***Hung.:*** Bucaine; Marcain; ***India:*** Marcain; Sensorcaine; ***Indon.:*** Bucain; Decain; Marcain; ***Irl.:*** Marcain; ***Israel:*** Kamacaine; Marcaine; ***Ital.:*** Bupibil; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Marcaina; ***Malaysia:*** Marcain; ***Mex.:*** Buvacaina; ***Neth.:*** Bupiforan; Marcaine; ***Norw.:*** Marcain; ***NZ:*** Marcain; ***Philipp.:*** Senpivac; Sensorcaine; ***Pol.:*** Marcaine; ***Port.:*** Bupinostrum; Marcaina; ***Rus.:*** Анекаин (Anekain); Bupicaine (Бупикаин)†; Marcain (Маркаин); ***S.Afr.:*** Macaine; Regibloc; ***Singapore:*** Marcain; ***Spain:*** Svedocain; ***Swed.:*** Marcain; ***Switz.:*** Carbostesin; Duracain; ***Thai.:*** Marcain; ***Turk.:*** Marcaine; ***UK:*** Marcain; ***USA:*** Marcaine; Sensorcaine; ***Venez.:*** Duracaina.

Multi-ingredient: ***Austral.:*** Marcain with Fentanyl; Marcain with Pethidine†; ***Fin.:*** Solomet c bupivacain hydrochlorid; ***NZ:*** Bupafen; Marcain with Fentanyl; ***USA:*** Duocaine.

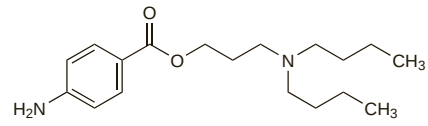
Butacaine Sulfate *(rINNM)*

Butacain. Sulph.; Butacaïne, Sulfate de; Butacaine Sulphate *(BANM)*; Butacaini Sulfas; Sulfato de butacaína. 3-Dibutylaminopropyl 4-aminobenzoate sulphate.

Бутакаина Сульфат

$(C_{18}H_{30}N_2O_2)_2,H_2SO_4$ = 711.0.

CAS — 149-16-6 (butacaine); 149-15-5 (butacaine sulfate).



(butacaine)

Profile

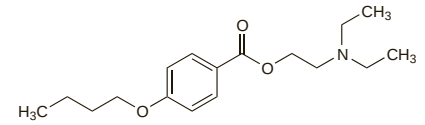
Butacaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) used for surface anaesthesia. It has been used topically, as the sulfate, in solutions for dental pain and in ear and nasal drops.

Butoxycaine Hydrochloride

Butoxicaína, hidrocloruro de; Butoxycaini Hydrochloridum. 2-Diethylaminoethyl-(*p*-butoxybenzoate) hydrochloride.

$C_{17}H_{27}NO_3,HCl$ = 329.9.

CAS — 3772-43-8 (butoxycaine); 2350-32-5 (butoxycaine hydrochloride).



(butoxycaine)

Profile

Butoxycaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) that has been used as the base or hydrochloride for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Bismolan†.