Precautions

As for Opioid Analgesics in general, p.103.

Abuse. There have been reports[1] of the abuse of dextropropoxyphene, and some[2] considered that the ready availability of dextropropoxyphene made it liable to abuse although it was a relatively weak opioid analgesic. However, others[3] thought there was no evidence that dextropropoxyphene was frequently associated with abuse, or concluded that, although there was abuse potential, it was of relatively low importance in terms of the community as a whole.[4]

A severe withdrawal syndrome has been reported[5] in an elderly patient who covertly consumed a daily dose of dextropropoxyphene of 1 to 3 g for at least 12 months. The patient was treated by a gradually decreasing dosage schedule of dextropropoxyphene over 9 weeks.

1. Tennant FS. Complications of propoxyphene abuse. *Arch Intern Med* 1973; **132:** 191–4.
2. Lader M. Abuse of weak opioid analgesics. *Hum Toxicol* 1984; **3** (suppl): 229S–36S.
3. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
4. Turner P. Final remarks. *Hum Toxicol* 1984; **3** (suppl): 237S–8S.
5. Hedenmalm K. A case of severe withdrawal syndrome due to dextropropoxyphene. *Ann Intern Med* 1995; **123:** 473.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving dextropropoxyphene, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of dextropropoxyphene in breast milk is too small to be harmful.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Porphyria. Dextropropoxyphene has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with opioid analgesics, see p.103.

Plasma concentrations of dextropropoxyphene are increased by ritonavir, with a resultant risk of toxicity; they should not be given together.

CNS depressants, including alcohol, may contribute to the hazards of dextropropoxyphene, see also Overdosage, above. The convulsant action of high doses of dextropropoxyphene may be enhanced by CNS stimulants.

Dextropropoxyphene interacts with several other drugs through inhibition of liver metabolism. Drugs reported to be affected include antidepressants (see p.379), benzodiazepines (see p.989), beta blockers (see p.1229), carbamazepine (see p.474), phenobarbital (see p.493), phenytoin (see p.497), and warfarin (see p.1427).

Antimuscarinics. A suggested interaction between *orphenadrine* and dextropropoxyphene has been questioned (see p.812).

Pharmacokinetics

Dextropropoxyphene is readily absorbed from the gastrointestinal tract, the napsilate tending to be more slowly absorbed than the hydrochloride, but both are subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 to 2.5 hours after ingestion. It is rapidly distributed and concentrated in the liver, lungs, and brain. About 80% of dextropropoxyphene and its metabolites are reported to be bound to plasma proteins. Dextropropoxyphene crosses the placenta. It has been detected in breast milk.

Dextropropoxyphene is *N*-demethylated to nordextropropoxyphene (norpropoxyphene) in the liver. It is excreted in the urine mainly as metabolites. It is now recognised that dextropropoxyphene and nordextropropoxyphene have prolonged elimination half-lives; values of 6 to 12 hours and 30 to 36 hours, respectively, have been reported. Accumulation of dextropropoxyphene and its metabolites may occur with repeated doses and nordextropropoxyphene may contribute to the toxicity seen with overdosage.

◊ Reviews.

1. Pearson RM. Pharmacokinetics of propoxyphene. *Hum Toxicol* 1984; **3** (suppl): 37S–40S.

The elderly. The elimination half-lives of dextropropoxyphene and its metabolite nordextropropoxyphene were prolonged in healthy elderly subjects when compared with young controls.[1] After multiple dosing median half-lives of dextropropoxyphene and nordextropropoxyphene were 36.8 and 41.8 hours, respectively in the elderly compared with 22.0 and 22.1 hours in the young subjects. In this study[1] there was a strong correlation between half-life of nordextropropoxyphene and estimated creatinine clearance.

1. Flanagan RJ, *et al.* Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989; **28:** 463–9.

Hepatic impairment. Plasma concentrations of dextropropoxyphene were higher in patients with cirrhosis given the drug than in healthy subjects whereas concentrations of nordextropropoxyphene were lower.[1]

1. Giacomini KM, *et al.* Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clin Pharmacol Ther* 1980; **28:** 417–24.

Renal impairment. Higher and more persistent plasma concentrations of dextropropoxyphene and nordextropropoxyphene in anephric patients when compared with healthy subjects[1] were attributed to decreased first-pass metabolism of dextropropoxyphene and decreased renal excretion of nordextropropoxyphene in the anephric patients.

1. Gibson TP, *et al.* Propoxyphene and norpropoxyphene plasma concentrations in the anephric patient. *Clin Pharmacol Ther* 1980; **27:** 665–70.

Uses and Administration

Dextropropoxyphene is an opioid analgesic (p.104) structurally related to methadone (p.82). It has mild analgesic activity and is given orally as the hydrochloride or napsilate to alleviate mild to moderate pain. Unlike the laevo-isomer (levopropoxyphene), dextropropoxyphene has little antitussive activity.

Dextropropoxyphene is mainly used with other analgesics that have anti-inflammatory and antipyretic effects, such as aspirin or paracetamol. In the USA the usual dose is 65 mg of the hydrochloride or 100 mg of the napsilate given every 4 hours up to a maximum total daily dose of 390 mg or 600 mg, respectively. In the UK similar doses have been given three or four times daily.

The combination preparation co-proxamol (dextropropoxyphene with paracetamol) has been gradually withdrawn from the UK market (see also Pain, below) although such combinations may remain available in a number of countries.

Pain. A detailed review[1] of the analgesic effectiveness of dextropropoxyphene suggested that with respect to single oral doses, recommended doses of dextropropoxyphene were no more (and probably less) effective than usual doses of paracetamol, aspirin, or other NSAIDs. However, the comparative effectiveness may vary substantially depending on the cause of the pain.

When it comes to comparative studies involving combinations of dextropropoxyphene with other analgesics, findings are even less clear-cut.[2] The effectiveness of co-proxamol has long been a matter of controversy yet despite this a survey[3] conducted in 30 UK teaching hospitals found that co-proxamol was the most widely used paracetamol-containing analgesic. It was suggested that the popularity of co-proxamol was purely down to prescribing habits passed on to new medical staff, rather than hard evidence regarding efficacy. This view has been refuted by others[4] who say that a large number of studies have shown clear analgesic effects for dextropropoxyphene. However, any assumption that the combination was widely used because it was more effective than paracetamol alone was not supported by a systematic overview of single-dose studies.[5] This concluded that while co-proxamol was indeed an effective analgesic it was no better than paracetamol alone. Although the evidence from this and other systematic reviews indicate that co-proxamol should be replaced by paracetamol alone for acute pain, the position for chronic use is considered to be not so clear (but see below).[6]

In January 2005, the UK CSM found the efficacy of co-proxamol to be poorly established and its risk of toxicity in overdose to be unacceptable;[7] they considered that there was no robust evidence of the superior efficacy of co-proxamol to full-strength paracetamol alone in either acute or chronic pain. Consequently, co-proxamol has been gradually withdrawn from the UK market. Fixed-dose combinations of dextropropoxyphene and paracetamol have also been withdrawn in several other countries including Sweden and Switzerland.

1. Beaver WT. Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review. *Hum Toxicol* 1984; **3** (suppl): 191S–220S.
2. Collins SL, *et al.* Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 26/06/08).
3. Haigh S. 12 Years on: co-proxamol revisited. *Lancet* 1996; **347:** 1840–1. Correction. *ibid.*; **348:** 346.
4. Sykes JV, *et al.* Coproxamol revisited. *Lancet* 1996; **348:** 408.
5. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997; **315:** 1565–71. Correction *ibid.* 1998; **316:** 116 and 656.
6. Anonymous. Co-proxamol or paracetamol for acute pain? *Drug Ther Bull* 1998; **36:** 80.
7. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)

Preparations

BP 2008: Co-proxamol Tablets; Dextropropoxyphene Capsules;
USP 31: Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Hydrochloride Capsules; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Acetaminophen Tablets; Propoxyphene Napsylate and Aspirin Tablets; Propoxyphene Napsylate Oral Suspension; Propoxyphene Napsylate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Gobbigesic; ***Austral.:*** Doloxene; ***Belg.:*** Depronal; ***Canad.:*** 642†; Darvon-N; ***Denm.:*** Abalgin; Doloxene; ***Fin.:*** Abalgin; ***Gr.:*** Romidon; Zideron; ***India:*** Parvodex; ***Irl.:*** Doloxene†; ***Ital.:*** Liberen†; ***Mex.:*** Darvon Simple; ***Neth.:*** Depronal; ***NZ:*** Doloxene†; ***S.Afr.:*** Doloxene; ***Spain:*** Darvon†; Deprancol; ***Swed.:*** Dexofen; Doloxene; ***USA:*** Darvon; Darvon-N.

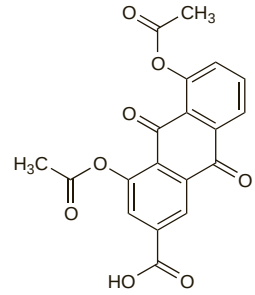
Multi-ingredient: ***Arg.:*** Artifene; Calmopirin; Canovex†; D-P†; Dexprofeno; Dextro + Dipirona; Dextrodip; Dorixina Forte; Gobbicalm; Klosidol; Klosidol B1 B6 B12; Supragesic; Vicefeno; ***Austral.:*** Capadex; Di-Gesic; Paradex; ***Austria:*** APA; Contraforte†; Sigmalin B forte; ***Belg.:*** Algophene; Distalgic†; ***Braz.:*** Doloxene-A; ***Fin.:*** Paraflex comp†; ***Fr.:*** Dextroref; Di Dolko; Di-Antalvic; Diadupsan†; Dialgirex; Dioalgo; Propofan; ***Hong Kong:*** Cosalgesic; Distalgesic†; Dolocin; Dolpocetmol; Medonol; ***Hung.:*** Novopyrin; ***India:*** Buta-Proxyvon; Ibu-Proxyvon; Parvon; Parvon Forte; Parvon-N; Parvon-Spas; Proxytab; Proxyvon; Spasmo-Proxyvon; Spasmocip; Spasmocip Plus; Sudhinol; Walagesic†; Wygesic; ***Irl.:*** Distalgesic†; ***Israel:*** Algolysin; Proxol; Rogaan; ***Mex.:*** Darvon-N Compuesto†; Neo-Percodan; Qual; ***Norw.:*** Aporex; ***NZ:*** Apo-Paradex†; Capadex; Paradex; ***Port.:*** Algifene; ***S.Afr.:*** Distalgesic; Doloxene Co; Doxyfene; Lentogesic; Synap; ***Swed.:*** Distalgesic†; Doleron†; Paraflex comp†; ***Switz.:*** Distalgesic†; ***UK:*** Cosalgesic†; Distalgesic†; ***USA:*** Balacet; Darvocet; Darvocet-N; Darvon Compound†; PC-Cap; Propacet; Trycet; Wygesic†.

Diacerein *(rINN)*

Diacereína; Diacéréine; Diacereinum; Diacerhein; Diacetylrhein; 2,4-dichlorobenzylique, alcool; Rhein Diacetate; SF-277; SF-277. 9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthroic acid diacetate.

Диацереин

$C_{19}H_{12}O_8$ = 368.3.
CAS — 13739-02-1.
ATC — M01AX21.
ATC Vet — QM01AX21.



Profile

Diacerein is an anthraquinone derivative that is used in osteoarthritis (p.11) in oral doses of 50 mg twice daily. Doses should be halved in patients with creatinine clearance less than 30 mL/minute. Diarrhoea is a common adverse effect with diacerein. Its active metabolite, rhein, a constituent of rhubarb (p.1768), is reported to act as an interleukin-1 inhibitor.

Administration in renal impairment. See above and Pharmacokinetics, below.

Musculoskeletal and joint disorders. Diacerein is thought to act via inhibition of interleukin-1β,[1] which plays a role in inflammatory processes. Systematic reviews[2,3] on the use of diacerein in the treatment of osteoarthritis have indicated that diacerein produces a small, but consistent, improvement in pain. Further research is necessary to confirm its short- and long-term effectiveness and safety but there is some evidence of residual benefit on stopping treatment,[3] which has been postulated to represent an improvement in the disease process.

1. Van den Berg WB. Les mécanismes d'action de la diacerhéine, premier inhibiteur de l'interleukine 1 dans l'arthrose. *Presse Med* 2004; **33:** 10–12.
2. Fidelix TSA, *et al.* Diacerein for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 06/10/06).
3. Rintelen B, *et al.* A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 2006; **166:** 1899–1906.

Pharmacokinetics. References.

1. Debord P, *et al.* Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 13–19.
2. Nicolas P, *et al.* Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; **35:** 347–59.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Artrodar; Artroglobina†; ***Austria:*** Artrolyt; Verboril; ***Braz.:*** Artrodar; ***Chile:*** Artrizona; ***Cz.:*** Artrodar; ***Fr.:*** Art; Zondar; ***Gr.:*** Arthrofar; Arthrorein; Deserein; Diacer; Diaceril; Idealite; Inflabion; Myobloc; Ostirein; Pentacrin; Reumanisal; Verboril; ***Indon.:*** Artrodar; ***Israel:*** Art; Diatrim; ***Ital.:*** Fisiodar; ***Malaysia:*** Artrodar; ***Port.:*** Artrolyt; Cartivix; ***Spain:*** Galaxdar; Glizolan; ***Thai.:*** Artrodar; ***Venez.:*** Artrodar.

Multi-ingredient: *Mex.:* Dolocartigen.

Diamorphine Hydrochloride

(BANM) ⊗

Diacetilmorfina, hidrocloruro de; Diacetylmorphine Hydrochloride; Heroin Hydrochloride; Hidrocloruro de diamorfina; Hidrocloruro de heroína. 4,5-Epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate.

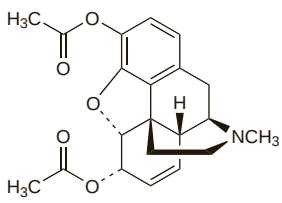
Героина Гидрохлорид; Диаморфина Гидрохлорид

$C_{21}H_{23}NO_5,HCl,H_2O$ = 423.9.

CAS — 561-27-3 (diamorphine); 1502-95-0 (diamorphine hydrochloride).

ATC — N02AA09.

ATC Vet — QN02AA09.



(diamorphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diamorphine:
57 Chevy; A Sidani; AIP; Al Capone; Amelia; Antifreeze; Aries; Aunt Hazel; Auntie Hazel; Aunty Hazel; Bacalhau; Bad bundle; Bad seed; Ball; Ballot; Bart Simpson; Batman; Beast; Big Bad Boy; Big bag; Big doodig; Big H; Big Harry; Bin laden; Bindle; Birdie powder; Black; Black Dragon; Black eagle; Black Girl; Black pearl; Black stuff; Black tar; Black tootsie roll; Blanche; Blanco; Blast; Bleue; Block busters; Blow; Blows; Blue bag; Blue hero; Blue star; Bobby Brown; Bomb; Bomba; Bombe; Bombido; Bombita; Bombitas; Bombs away; Bone; Bonita; Boy; Bozo; Brad; Brain damage; Brea; Brick gum; Broja; Brother; Brown; Brown crystal; Brown rhine; Brown sugar; Brown tape; Bugger; Bull dog; Bundle; Burra; Butu; Caballo; Caca; Calbo; Capital H; Caps; Captain Jack; Carga; Carne; Cavalo; Chang; Chapopote; Charley; Chatarra; Cheese; Cheva; Cheval; Chi; Chiba; Chick; Chicken; Chicle; Chieva; China cat; China white; Chinche; Chinese H; Chinese red; Chinese Rocks; Chinoise; Chip; Chiva; Chocofan; Choco-fan; Chueva; Chunks; Climax; Cocofan; Coffee; Cotics; Cotton Candy; Courage pills; Crank; Crap; Crop; Crown crap; Cura; Dead on arrival; Dead president; Deuce; Diesel; Diggidy; Dirt; DOA; Dog food; Dogee; Dogie; Doogie; Doojee; Dookey Rocks; Dooley; Doosey; Dope; Downtown; Dr. Feelgood; Dragon; Dreck; DT; Dugee; Dugie; Duji; Dujra; Dujre; Dust; Dyno; Dyno-pure; Eggs; Eight; Eighth; Elephant; Estuffa; Fachiva; Ferry dust; Fix; Flea powder; Foil; Foo foo stuff; Foolish powder; Furra; Galloping horse; Gallup; Gamot; Garbage; Gato; Gear; George; George smack; Ghost; Girl; Glacines; Glass; Goat; Gold; Golden Brown; Golden girl; Golpe; Goma; Good; Good H; Good Horse; Good and plenty; Goods; Goop; Grape Jolly Rancher; Gravy; Grey shields; H; H22; H-bomb; H Caps; Hache; Hair; Hairpiece; Hairy; Hammer; Hard candy; Hard stuff; Harriet Tubman; Harry; Harry Jones; Hayron; Hazel; Heaven; Heaven dust; Heavy stuff; Helen; Hell dust; Henry; Hera; Hero; Hero of the underworld; Heroa; Heroina; Heron; Herone; Hessle; Him; Holy terror; Hombre; Homebake; Homicide; Hong-yen; Hood; Hop; Horning; Horse; Horsebite; Hot dope; Hot heroin; HRN; Isda; Jack; Jee gee; Jerry Springer; Jesus; Jive; Jive doo jee; Joharito; Jojee; Jones; Joy; Joy dust; Joy flakes; Joy powder; Judas; Junco; Junk; Kabayo; Kaka Water; Karachi; Kermit the Frog; La Buena; La Chiva; Lady H; Layne; LBJ; Lemonade; Life saver; Little bomb; Man; Manteca; Matsakow; Mayo; Mexican Black Tar; Mexican brown; Mexican Dirt; Mexican horse; Mexican mud; Mister Brownstone; Mojo; Money talks; Monkey; Montego; Morse Code Features; Morotgara; Mortal combat; Mother pearl; Mr. Brownstone; Mud; Murotugora; Muzzle; Nanoo; Nice and easy; Nickel bag; Nickel deck; Nixon; Noddy Brown; Noise; Nose; Nose drops; Number 3; Number 4; Number 8; Nurse; Oddy Noddy; Of course my horse; Ogoy; Oil; Old garbage; Old navy; Old Steve; One way; Orange line; Outfit; Pack; Pakistanaise; Pako; Pangonadalot; Parachute; P-dope; Peg; Pepper; Perfect high; P-funk; Pluto; Po; Poeira; Poison; Polvo; Poppy; Poudre; Powder; Predator; Primo; Produto; Pulborn; Pure; Quill; Race horse Charlie; Racehorse Charlie; Ragweed; Rain; Rambo; Rane; Raw; Raw fusion; Raw hide; Raw Opportunities; Ready rock; Red chicken; Red devil; Red eagle; Red rock; Red rum; Reindeer dust; Rhine; Ring of Turd; Rob Flaherty; Rock; Rocks; Rush hour; Sack; Salt; Scag; Scat; Scate; Schmack; Schmeck; Schmeek; Scott; Scramble; Second to none; Shit; Shmeck; Shmeek; Shmek; Shoot; Silk; Skag; Skid; Skunk; Slack-dad-eat-your-heart-out; Slam; Sleeper; Sleepers; Slime; Slow; Sludge; Smack; Snotty; Snow; Spider; Spider blue; Stuff; Stunna; Sugar; Suicide; Sweet dreams; Sweet Jesus; Sweet stuff; Synthe; Tang; Tar; Taste; Tecata; Tecate; Thailandaise; Thanie; The beast; The fake throwdown; The Jack Bauer; The Loud-House Permadillo; The Nax; The witch; Thing; Thunder; Tiger; Tigre; Tigre Blanco; Tigre del Norte; Tits; TNT; T.N.T.; Tongs; Tootsie roll; Top drool; Train; Trash; Twin towers; Twists; Vidrio; Whack; Whicked; White; White Bitch; White boy; White dragon; White dynamite; White girl; White horse; White junk; White lady; White nurse; "White Pony"; White stuff; White Tiger; Wicked; Wings; Witch; Witch hazel; WTC; Zoquete.

Pharmacopoeias. In *Br.* and *Swiss*. *Swiss* also includes the anhydrous form.

BP 2008 (Diamorphine Hydrochloride). A white or almost white crystalline powder, odourless when freshly prepared but develops an odour characteristic of acetic acid on storage. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether. Protect from light.

Incompatibility. Diamorphine hydrochloride is incompatible with mineral acids and alkalis and with chlorocresol.[1]

The *BNF* notes that cyclizine may precipitate from mixtures with diamorphine hydrochloride at concentrations of cyclizine greater than 10 mg/mL, or in the presence of sodium chloride 0.9%, or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.

It also considers that mixtures of diamorphine and haloperidol are liable to precipitate after 24 hours if the haloperidol concentration is above 2 mg/mL. Under some conditions mixtures of metoclopramide and diamorphine may become discoloured and should be discarded.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.

Stability. Diamorphine is relatively unstable in aqueous solution and is hydrolysed to 6-*O*-monoacetylmorphine and then morphine to a significant extent at room temperature; 3-*O*-monoacetylmorphine is only occasionally detected. The rate of decomposition is at a minimum at about pH 4.[1,2]

In a study of the stability of aqueous solutions of diamorphine in chloroform water it was concluded that such solutions should be used within 3 weeks of preparation when stored at room temperature.[3] Another study[4] noted that the degradation products of diamorphine were not devoid of analgesic activity. Using a more sensitive analytical method it was reported that although the pH range of maximum stability of diamorphine in aqueous solution was 3.8 to 4.4, the addition of buffers reduced stability.[5] Simple unbuffered chloroform water gave maximum stability, the shelf-life of such a solution being 4 weeks at room temperature.

The BP 2008 recommends that solutions for injection be prepared immediately before use by dissolving Diamorphine Hydrochloride for Injection in Water for Injections. This may pose a problem with solutions for subcutaneous infusion when concentrated solutions may remain in infusion pump reservoirs for some time.[6] Investigation of 9 concentrations of diamorphine stored at 4 different temperatures for 8 weeks[7] revealed instability under conditions of concentration, time, and temperature prevalent during subcutaneous infusion. Degradation of diamorphine occurred at all concentrations (0.98 to 250 mg/mL) at temperatures of 4° and above; the effect of temperature was significant at 21° and 37°. The percentage fall in diamorphine concentration was directly related to initial concentration and was accompanied by a corresponding increase in 6-*O*-monoacetylmorphine and, to a lesser extent, morphine; other possible breakdown products such as 3-*O*-monoacetylmorphine were not present in detectable quantities. Diamorphine degradation was associated with a fall in pH and the development of a strong acetic acid-like odour. Precipitation and a white turbidity was seen in solutions of 15.6 mg/mL and above after incubation for 2 weeks at 21° and 37°. It has been noted that solutions for infusion are generally freshly prepared and used within 24 hours, but that signs of precipitation should be watched for, especially when using longer-term infusions and high concentrations of diamorphine.[7]

In another stability study[8] diamorphine hydrochloride in concentrations of both 1 and 20 mg/mL in sodium chloride 0.9% was stable for a minimum of 15 days at room temperature (23° to 25°) and 4° when stored in a PVC container. In one type of disposable infusion device (Infusor) similar solutions were stable for 15 days even at 31°. In another infusion device (Intermate 200) diamorphine was stable for a minimum of 15 days at both concentrations and all temperatures except for the 1 mg/mL solution kept at 31° when stability was only maintained for a minimum of 2 days. When stored in glass syringes both strengths of diamorphine hydrochloride were stable for 15 days at 4° and at room temperature the 1 mg/mL solution was stable for a minimum of 7 days and the 20 mg/mL solution was stable for a minimum of 12 days. There were no substantial changes in physical appearance or pH.

1. Davey EA, Murray JB. Hydrolysis of diamorphine in aqueous solutions. *Pharm J* 1969; **203:** 737.
2. Davey EA, Murray JB. Determination of diamorphine in the presence of its degradation products using gas liquid chromatography. *Pharm J* 1971; **207:** 167.
3. Cooper H, *et al.* Stability of diamorphine in chloroform water mixture. *Pharm J* 1981; **226:** 682–3.
4. Twycross RG. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 218.
5. Beaumont IM. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 41.
6. Jones VA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *Br J Clin Pharmacol* 1987; **23:** 651P.
7. Omar OA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; **41:** 275–7.
8. Kleinberg ML, *et al.* Stability of heroin hydrochloride in infusion devices and containers for intravenous administration. *Am J Hosp Pharm* 1990; **47:** 377–81.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Diamorphine is subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Diamorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, below).

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts. Nausea and hypotension are claimed to be less common than with morphine.

There are many reports of adverse effects associated with the abuse of diamorphine, usually obtained illicitly in an adulterated form.

Abuse. Most of the reports of adverse effects with diamorphine involve its abuse. In addition to the central effects, there are effects caused by the administration methods and by the adulterants.[1,2] Thus in many instances it is difficult to identify the factor causing the toxicity. Most body systems are involved including the immune system,[3] kidneys,[4,5] liver,[6] respiratory system,[7-10] and the nervous system.[11-16]

Other aspects of the illicit use of diamorphine include fatal overdose[17] and smuggling by swallowing packages of drug[18,19] or other methods of internal bodily concealment.

1. Hendrickse RG, *et al.* Aflatoxins and heroin. *BMJ* 1989; **299:** 492–3.
2. CDC. Atypical reactions associated with heroin use: five states, January–April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.*; 852.
3. Husby G, *et al.* Smooth muscle antibody in heroin addicts. *Ann Intern Med* 1975; **83:** 801–5.
4. Cunningham EE, *et al.* Heroin-associated nephropathy. *JAMA* 1983; **250:** 2935–6.
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