Buprenorphine *(BAN, rINN)* ⊗

Buprenorfiini; Buprenorfin; Buprenorfina; Buprenorfinas; Buprénorphine; Buprenorphinum; RX-6029-M. (6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-*O*-methyl-6,14-ethano-17-normorphine; (2*S*)-2-[(−)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3,3-dimethylbutan-2-ol.

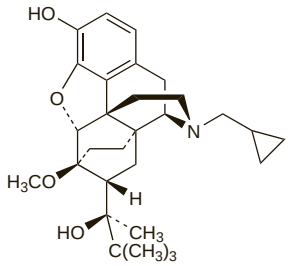
Бупренорфин

$C_{29}H_{41}NO_4$ = 467.6.

CAS — 52485-79-7.

ATC — N02AE01; N07BC01.

ATC Vet — QN02AE01; QN07BC01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of buprenorphine: TEM; Tems.

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

Ph. Eur. 6.2 (Buprenorphine). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in acetone; slightly soluble in cyclohexane; soluble in methyl alcohol. It dissolves in dilute solutions of acids. Protect from light.

Buprenorphine Hydrochloride

(BANM, USAN, rINNM) ⊗

Buprenorfiinihydrokloridi; Buprenorfin-hidroklorid; Buprenorfinhydrochlorid; Buprenorfinhydroklorid; Buprenorfino hidrochloridas; Buprénorphine, chlorhydrate de; Buprenorphini hydrochloridum; CL-112302; Hidrocloruro de buprenorfina; NIH-8805; UM-952.

Бупренорфина Гидрохлорид

$C_{29}H_{41}NO_4$,HCl = 504.1.

CAS — 53152-21-9.

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

Ph. Eur. 6.2 (Buprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in cyclohexane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Buprenorphine Hydrochloride). pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Buprenorphine may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, below). Abrupt withdrawal of buprenorphine is said to produce only a mild abstinence syndrome, which may be delayed in onset.

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

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Acute hepatotoxicity, including elevated liver enzyme values, hepatitis with jaundice, hepatic failure, necrosis, and encephalopathy, and hepatorenal syndrome, has been reported in opioid-dependent addicts; these reactions have also occurred after the misuse of buprenorphine, particularly after high doses or intravenous use.

Local reactions such as rash, erythema, and itching have been reported with the transdermal patches. In isolated cases delayed local allergic reactions with marked signs of inflammation have occurred; the patches should be withdrawn in such cases.

Treatment of adverse effects is similar to that for other opioid analgesics (p.102). The effects of buprenorphine are only partially reversed by naloxone (see Effects on the Respiratory System, below) but use of the latter is still recommended.

Incidence of adverse effects. Adverse effects reported[1] after *parenteral* buprenorphine in 8187 patients were nausea (8.8%), vomiting (7.4%), drowsiness (4.3%), sleeping (1.9%), dizziness (1.2%), sweating (0.98%), headache (0.55%), confusion (0.53%), lightheadedness (0.38%), blurred vision (0.28%), euphoria (0.27%), dry mouth (0.11%), depression (0.09%), and hallucinations (0.09%). Some studies[2,3] have reported nausea, vomiting, and dizziness to be more troublesome with buprenorphine than with morphine.

In a study[4] of *sublingual* buprenorphine, 50 of 141 cancer patients withdrew because of adverse effects, especially dizziness, nausea, vomiting, and drowsiness; constipation was not reported. A woman developed[5] a painless ulcer on the upper surface of her tongue after she had put sublingual buprenorphine tablets on rather than under her tongue.

Shock occurred[6] in 2 patients 2 hours after receiving *epidural* buprenorphine 300 micrograms; treatment with naloxone was unsuccessful but symptoms disappeared spontaneously after 2 to 3 hours.

In a multicentre study[7] of *transdermal* buprenorphine, 252 of 1223 patients with moderate to severe cancer pain or non-cancer pain withdrew due to adverse effects. The most commonly reported were nausea (11%), vomiting (9.2%), constipation (7.8%), dizziness (7.5%), drowsiness (4.0%), retching (3.7%), generalised pruritus (2.0%), and headache (1.6%); local adverse effects included pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%). Another study[8] reported oedema, headache, nausea, palpitation, and difficulty concentrating as causes for therapy withdrawal in 4 out of 90 patients.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Sear JW, *et al.* Buprenorphine for postoperative analgesia. *Br J Anaesth* 1979; **51:** 71.
3. Kjaer M, *et al.* A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. *Br J Clin Pharmacol* 1982; **13:** 487–92.
4. Robbie DS. A trial of sublingual buprenorphine in cancer pain. *Br J Clin Pharmacol* 1979; **7** (suppl 3): 315S–317S.
5. Lockhart SP, Baron JH. Tongue ulceration after lingual buprenorphine. *BMJ* 1984; **288:** 1346.
6. Christensen FR, Andersen LW. Adverse reaction to extradural buprenorphine. *Br J Anaesth* 1982; **54:** 476.
7. Muriel C, *et al.* Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther* 2005; **27:** 451–62.
8. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; **26:** 1808–20.

Effects on the heart. For a report of myocardial infarction associated with abuse of buprenorphine, see Abuse under Precautions, below.

Effects on mental function. Psychotomimetic effects have been relatively uncommon with buprenorphine. Hallucinations were reported[1] in only 7 of 8147 patients (0.09%) given buprenorphine by injection. There have been reports of hallucinations after sublingual[2] or epidural[3] use.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Paraskevaides EC. Near fatal auditory hallucinations after buprenorphine. *BMJ* 1988; **296:** 214.
3. MacEvilly M, O'Carroll C. Hallucinations after epidural buprenorphine. *BMJ* 1989; **298:** 928–9.

Effects on the respiratory system. There have been varying reports on the occurrence of respiratory depression with buprenorphine. It may be subject to a 'ceiling effect' in which respiratory depression does not increase further above doses of about 3 micrograms/kg.[1] However, high doses of 30 or 40 micrograms/kg given as sole intravenous analgesic in balanced anaesthesia have been associated with severe respiratory depression.[2]

Respiratory depression may be delayed in onset and more prolonged than with morphine and is only partially reversed by naloxone, possibly because buprenorphine is very firmly bound to opioid receptors. A study of sublingual buprenorphine for postoperative pain relief was abandoned when 3 of the first 16 patients showed signs of late-onset respiratory depression after the second dose of buprenorphine; the respiratory depression did not respond to naloxone.[3] Successful reversal has been shown in healthy subjects with buprenorphine-induced respiratory depression given large doses of naloxone 5 or 10 mg, but not with 1 mg; reversal was gradual in onset and decreased the duration of the normally prolonged respiratory depression.[4] Other studies found that lower doses of naloxone 2 to 4 mg given over 30 minutes,[5,6] or bolus doses of 2 to 3 mg followed by a continuous infusion of 4 mg/hour,[6] were effective in reversing buprenorphine-induced respiratory depression. The authors of both these studies suggested that a longer duration of naloxone infusion may be needed for reversal of respiratory depression caused by high doses of buprenorphine. The respiratory depressant and analgesic effects of buprenorphine were decreased by the *concomitant* use of naloxone.[7] It should be noted that a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

1. Dahan A, *et al.* Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; **94:** 825–34.
2. Schmidt JF, *et al.* Postoperative pain relief with naloxone: severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia* 1985; **40:** 583–6.
3. Thörn S-E, *et al.* Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet* 1988; **i:** 179–80.
4. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 1989; **45:** 66–71.
5. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med* 2006; **20** (Suppl 1): s3–s8.
6. van Dorp E, *et al.* Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 2006; **105:** 51–7.
7. Lehmann KA, *et al.* Influence of naloxone on the postoperative analgesic and respiratory effects of buprenorphine. *Eur J Clin Pharmacol* 1988; **34:** 343–52.

Overdosage. A small case series reported[1] acute buprenorphine intoxication in 5 children, aged from 15 to 22 months, after accidental ingestion of sublingual tablets; of these, 4 had ingested a combined preparation containing naloxone (*Suboxone; Reckitt Benckiser, USA*). Symptoms included drowsiness and miosis; decreased respiratory rates were reported in 4. All 5 children required hospital admission; 4 were treated with naloxone and 1 needed mechanical ventilation. Accidental poisoning has also been reported[2] in a 9-month-old infant who ingested *Suboxone*; his symptoms were reversed by naloxone. A retrospective review[3] of buprenorphine overdoses in children under 6 years of age reported by US poison centres to a national surveillance system from November 2002 to December 2005 concluded that overdosage is generally well tolerated. Out of 86 reports, 54 children developed symptoms of toxicity. Such symptoms included: drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities, and significant CNS and respiratory depression occurred in 7%. *Suboxone* preparations were the most commonly ingested products. The authors considered that any child who has ingested more than 2 mg and any aged under 2 years who has had more than a lick or taste should be referred to the emergency department.

During the years 1980 to 2002, buprenorphine was mentioned in 43 cases of adult fatalities in the UK.[4] Of these, 27 deaths were confirmed to have involved buprenorphine including 7 cases where it was taken alone. In those deaths where multiple drugs were involved sedatives or benzodiazepines were detected in 23 cases and other opioids were found in 17 cases; alcohol had also been taken in 10 cases. The authors also found an increase in buprenorphine-related fatalities since 1999 when the high-dose formulation became available.

1. Geib A-J, *et al.* Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics* 2006; **118:** 1746–51.
2. Cho CS, *et al.* Exploratory buprenorphine ingestion in an infant. *Ann Emerg Med* 2006; **48:** 109.
3. Hayes BD, *et al.* Toxicity of buprenorphine overdoses in children. *Pediatrics* 2008; **121:** 807–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/4/e782 (accessed 22/07/08)
4. Schifano F, *et al.* Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. *Hum Psychopharmacol* 2005; **20:** 343–8.

Precautions

As for Opioid Analgesics in general, p.103.

Buprenorphine has opioid antagonist actions and may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

Respiratory depression, if it occurs, is relatively slow in onset and of prolonged duration; it may be only partially reversed by naloxone.

Licensed product information states that baseline liver function levels should be established before starting buprenorphine therapy, and periodic monitoring of liver function should be performed throughout therapy in patients being treated for opioid dependence. It should be used with caution in all patients with pre-existing hepatic impairment.

Absorption of buprenorphine from transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take up to 30 hours for plasma concentrations of buprenorphine to decrease by 50% after removal of a patch; patients who have had adverse effects should be monitored during this period.

Abuse. A 22-year-old man had chest pains on each of two occasions after he had inhaled crushed buprenorphine tablets.[1] An ECG taken after the second episode suggested that the patient had suffered a myocardial infarction. Intravenous injection of crushed sublingual tablets was associated with rhabdomyolysis and sciatic neuropathy in 2 patients.[2] A case series[3] of 4 patients

reported severe limb and digit complications, such as ischaemia and gangrene, from parenteral abuse of sublingual buprenorphine tablets; intra-arterial injection in 2 cases resulted in amputation of the affected digits or limb. The use of adulterants in illicit preparations may also cause adverse effects: 4 patients on substitution treatment developed candida endophthalmitis after intravenously injecting sublingual buprenorphine diluted with lemon juice.[4]

Hepatotoxicity has been seen in opioid-dependent addicts after buprenorphine abuse (see Adverse Effects and Treatment, above).

1. Cracowski J-L, *et al.* Myocardial infarction associated with buprenorphine. *Ann Intern Med* 1999; **130:** 537.
2. Seet RCS, Lim ECH. Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy. *Ann Emerg Med* 2006; **47:** 396–7.
3. Loo HW, *et al.* Severe upper limb complications from parenteral abuse of Subutex. *Ann Acad Med Singapore* 2005; **34:** 575–8.
4. Cassoux N, *et al.* Presumed ocular candidiasis in drug misusers after intravenous use of oral high dose buprenorphine (Subutex). *Br J Ophthalmol* 2002; **86:** 940–1.

Breast feeding. From a study[1] of a breast-feeding mother who was receiving buprenorphine 4 mg daily, it was estimated that at the age of 4 weeks the total amount ingested by the infant during a 24-hour period was 3.28 micrograms for buprenorphine and 0.33 micrograms for norbuprenorphine. Another study[2] found that buprenorphine was present in the breast milk of a breast-feeding mother with a maternal milk-to-plasma ratio of about one. The authors of both studies considered the amount absorbed through breast feeding to be low.

The *BNF* and some licensed product information states that buprenorphine should not be given to mothers who are breast feeding.

Studies in *rats* have shown that it may inhibit lactation.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Johnson RE, *et al.* Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001; **63:** 97–103.

Pregnancy. An infant born to a mother who was being treated with buprenorphine 4 mg daily for diamorphine addiction suffered a minor withdrawal syndrome 2 days after birth.[1] The infant rapidly recovered without any treatment. No further signs of withdrawal occurred when breast feeding was abruptly stopped at the age of 8 weeks. In another report[2] of 15 opioid-dependent mothers who had received buprenorphine maintenance during their pregnancies, withdrawal symptoms were either absent or mild in 12 of the neonates. The remaining 3 neonates required treatment with morphine. There appeared to be no correlation between the buprenorphine dose and the degree of withdrawal symptoms. A literature review[3] found that of about 309 infants born to opioid-dependent mothers maintained on buprenorphine (sublingual dose range: 0.4 to 24 mg daily), 193 developed neonatal abstinence syndrome; of these, 149 required treatment. More than 40% of treated cases were confounded by misuse of other drugs. Onset of symptoms occurred within the first 12 to 48 hours and peaked within about 72 to 96 hours; duration of symptoms was about 120 to 168 hours although in some infants, it was reported to last for 6 to 10 weeks.

The 67 pregnancies of 66 women using buprenorphine have been followed in a prospective study.[4] The incidences of premature birth, caesarean section, and low Apgar scores in buprenorphine-exposed neonates were no greater than those seen in the general population although the mean birth-weight of the exposed neonates was significantly lower. In the exposed group, 91% of neonates needed intensive care treatment: 76% had neonatal abstinence syndrome and 57% needed opioid replacement therapy. There were also 2 cases of sudden infant deaths in the exposed group, which was considered to be higher than that generally expected.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Fischer G, *et al.* Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 2000; **95:** 239–44.
3. Johnson RE, *et al.* Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 2003; **70** (suppl 2): S87–S101.
4. Kahila H, *et al.* A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. *Acta Obstet Gynecol Scand* 2007; **86:** 185–90.

Interactions

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

Buprenorphine is metabolised by the cytochrome P450 isoenzyme CYP3A4; consequently, use with other drugs that induce or inhibit this isoenzyme may result in changes in plasma concentrations of buprenorphine and, possibly adverse effects. Some manufacturers state that dosage adjustment of buprenorphine may be necessary when used with such drugs. The UK licensed product information for one sublingual formulation (*Subutex; Schering-Plough*) recommends that the dose of buprenorphine should be halved when starting treatment with the potent CYP3A4 inhibitor, ketoconazole.

There have been reports of respiratory and cardiovascular collapse in patients given therapeutic doses of intravenous buprenorphine and diazepam.

Use with other potentially hepatotoxic drugs may increase the risk of liver damage.

Analgesics. There is a risk that, with opioid agonist-antagonists such as buprenorphine, their antagonistic effects might impair more effective analgesic therapy. This appeared to happen in 2 cancer patients both of whom were given sublingual buprenorphine that was later substituted by *morphine*.[1] Conventional doses of morphine were inadequate and in one patient raising the dose of morphine proved fatal.

1. Overweg-van Kints J, Stricker BHC. Falende pijnbestrijding tijdens sublinguaal gebruik van buprenorfine. *Ned Tijdschr Geneeskd* 1987; **131:** 1973–4.

Antivirals. Various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and most are also substrates for CYP3A4; thus, they have the potential to interact with buprenorphine. A pharmacokinetic study[1] found that usual doses of *nelfinavir, ritonavir,* and *lopinavir-ritonavir* given to HIV-negative patients taking buprenorphine with naloxone for opiate dependence did not produce any clinically significant interactions: ritonavir increased the area under the concentration-time curve (AUC) of buprenorphine by about 57%, although no adverse effects were seen. Another pharmacokinetic study[2] in a similar group of patients also found no clinically significant interactions between buprenorphine with naloxone and *delavirdine* or *efavirenz*: delavirdine increased the AUC of buprenorphine fourfold, and efavirenz decreased it by about 50%, but no adverse effects were seen. However, a small case series[3] of 3 opioid-dependent patients reported symptoms of buprenorphine toxicity, such as dizziness, daytime somnolence, and decreased mental functioning, with concomitant *atazanavir* and ritonavir therapy.

Buprenorphine does not appear to significantly affect the pharmacokinetics of antiretrovirals.[1,2]

1. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: I—The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis* 2006; **43** (suppl 4): S224–S234.
2. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: II—The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. *Clin Infect Dis* 2006; **43** (suppl 4): S235–S246.
3. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. *AIDS* 2006; **20:** 783–4.

Pharmacokinetics

After intramuscular injection, buprenorphine rapidly reaches peak plasma concentrations. Absorption also takes place through the buccal mucosa after sublingual doses and peak plasma concentrations are achieved after 90 minutes. Transdermal application results in absorption through the skin; the minimum effective concentration is reached in 12 to 24 hours and peak plasma concentrations are achieved after about 60 hours. However, there is a lack of correlation between plasma concentrations and analgesic activity. Buprenorphine is about 96% bound to plasma proteins.

Elimination of buprenorphine is bi- or triphasic; metabolism takes place in the liver by oxidation via the cytochrome P450 isoenzyme CYP3A4 to the pharmacologically active metabolite *N*-dealkylbuprenorphine (norbuprenorphine), and by conjugation to glucuronide metabolites. Buprenorphine is subject to considerable first-pass metabolism after oral doses. However, when given by the usual routes buprenorphine is excreted mainly unchanged in the faeces; there is some evidence for enterohepatic recirculation. Plasma elimination half-lives have ranged from 1.2 to 7.2 hours after intravenous injection; elimination half-lives after sublingual or transdermal use are longer and may range from 20 to 36 hours or more. Metabolites are excreted in the urine, but very little unchanged drug is excreted in this way. Buprenorphine crosses the placenta and small amounts are distributed into breast milk.

◊ References.

1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005; **44:** 661–80.

Administration. ***BUCCAL ROUTE.*** Absorption of sublingual buprenorphine is relatively slow. In a 10-hour study[1] plasma concentrations after 400 or 800 micrograms given sublingually peaked at about 200 minutes (range 90 to 360 minutes) and buprenorphine was still detected in plasma at the end of the study. Systemic availability was about 55% (range 16 to 94%) and absorption was more or less complete 5 hours after a dose. However, the authors of a subsequent study[2] considered that this was an overestimation, possibly due to methodological flaws. The later study results indicated that the bioavailability of sublingual buprenorphine is about 30% and that sublingual holding times between 3 and 5 minutes are bioequivalent. Another single-dose study[3] found that the bioavailability of sublingual buprenorphine was 50% less from a tablet than from a liquid formulation. Later studies[4,5] noted that the bioavailability of buprenorphine from a sublingual tablet relative to a sublingual liquid formulation was about 70% after daily dosing for 7 days. One of these studies[4] also found that the bioavailability of sublingual buprenorphine from a tablet formulation containing naloxone was higher than from a single-ingredient tablet formulation and similar to that seen with liquid formulations.

1. Bullingham RES, *et al.* Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982; **13:** 665–73.
2. Mendelson J, *et al.* Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; **37:** 31–7.
3. Nath RP, *et al.* Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol* 1999; **39:** 619–23.
4. Strain EC, *et al.* Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend* 2004; **74:** 37–43.
5. Compton P, *et al.* Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug Alcohol Depend* 2006; **82:** 25–31.

Children. The terminal elimination half-life of buprenorphine was only about 1 hour in small children aged 4 to 7 years given 3 micrograms/kg intravenously as premedication, but could not be estimated reliably because of the rapid decline in plasma-buprenorphine concentrations.[1] Clearance values did, however, appear higher than in adults; steady-state volume of distribution was similar. Premature neonates (gestational age 27 to 32 weeks) given a similar dose followed by an infusion of 0.72 micrograms/kg per hour had a considerably lower clearance rate and had a mean elimination half-life of 20 hours.[2] Although this dosing regimen appeared to be safe, sedation was judged to be inadequate in 4 of the 12 neonates studied. It was suggested that as buprenorphine given by infusion might not produce consistent sedation and analgesia in premature neonates, it could not be recommended for use in neonatal care.

1. Olkkola KT, *et al.* Pharmacokinetics of intravenous buprenorphine in children. *Br J Clin Pharmacol* 1989; **28:** 202–4.
2. Barrett DA, *et al.* The pharmacokinetics and physiological effect of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol* 1993; **36:** 215–19.

Renal impairment. Buprenorphine clearance appears to occur mainly by hepatic extraction and metabolism and would not be expected to be related to renal function, whereas metabolites are excreted in urine. In a study, buprenorphine kinetics were similar in anaesthetised healthy patients to those in patients with renal impairment, with a mean elimination half-life of 398 and 239 minutes, respectively.[1] Plasma concentrations of the metabolites norbuprenorphine and buprenorphine-3-glucuronide were increased about 4 times and 15 times, respectively in patients with renal impairment,[1] but significant pharmacological activity was unlikely since norbuprenorphine has little analgesic activity compared with the parent compound and buprenorphine-3-glucuronide has none.

1. Hand CW, *et al.* Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 1990; **64:** 276–82.

Uses and Administration

Buprenorphine is an opioid analgesic (p.104) classified as an opioid agonist and antagonist. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Buprenorphine is also used in the treatment of opioid dependence.

Buprenorphine has a relatively slow onset but prolonged duration of action. On intramuscular injection analgesia is apparent within 15 minutes and lasts up to 6 hours. A slower, more prolonged response is achieved after sublingual doses. The analgesic effects of buprenorphine after transdermal application may not be seen for at least 12 to 24 hours or up to 72 hours in the case of the once-weekly patch.

Buprenorphine is usually given by intramuscular or intravenous injection or sublingually as the hydrochloride or as transdermal patches as the base. For all routes doses are expressed in terms of the base. Buprenor-

phine hydrochloride 107.8 micrograms is equivalent to about 100 micrograms of buprenorphine.

Buprenorphine is given by all the above routes for opioid analgesia in moderate to severe **pain**.

- The dose by intramuscular or slow intravenous injection is 300 to 600 micrograms repeated every 6 to 8 hours as required
- By the sublingual route, doses of 200 to 400 micrograms may be repeated every 6 to 8 hours as required
- For opioid treatment of chronic pain in patients aged 18 years and over transdermal patches delivering varying amounts of buprenorphine are available. Doses should be individually titrated for each patient according to previous opioid usage. During transfer to treatment with buprenorphine patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-buprenorphine concentrations. Depending on dose required up to 2 patches may be applied, however, this should be done at the same time to avoid confusion. Buprenorphine patches are not appropriate for acute pain. In the UK, transdermal buprenorphine patches are available as follows:

  Transtec (*Napp, UK*) delivering buprenorphine in a range of 35 to 70 micrograms/hour. Initial dosages should not exceed 35 micrograms/hour in *opioid-naive* patients. For *patients who have been receiving a strong opioid analgesic* the initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 35 micrograms/hour of buprenorphine is roughly equivalent to 30 to 60 mg daily of oral morphine sulfate. Patches should be replaced every 96 hours at the latest with the new patch being applied to a different site; use of the same area of the skin should be avoided for at least the next 2 applications.

  BuTrans (*Napp, UK*) delivering buprenorphine in a range of 5 to 20 micrograms/hour. Initial dosages should not exceed 5 micrograms/hour in *all* patients. Patches should be replaced every 7 days with the new patch being applied to a different site; use of the same area of the skin should be avoided for the next 3 to 4 weeks.

When used in balanced **anaesthesia** 300 micrograms may be given intramuscularly or 400 micrograms sublingually for premedication; 300 to 450 micrograms may be given intravenously as a perioperative analgesic supplement.

For the treatment of **opioid dependence** in patients aged 16 years and over, the initial dose is 0.8 to 4 mg sublingually once daily. The dose may be increased as necessary but maintenance doses should not exceed 32 mg daily. Once the patient has been stabilised, the dosage should be reduced gradually to a lower maintenance dose; treatment may eventually be stopped if appropriate. For addicts who have not undergone opioid withdrawal before starting buprenorphine, the first dose of buprenorphine should not be given until the first signs of craving appear or until at least 4 (USA) or 6 (UK) hours after the last opioid use. In those already receiving methadone replacement, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine therapy. As a deterrent to abuse, a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

For details of doses in **children**, see below.

Action. Buprenorphine is generally described as a mixed agonist-antagonist acting mainly as a partial agonist at μ opioid receptors, with some antagonist activity at κ receptors. It has also been shown to bind at μ, δ, and κ opioid binding sites and to have high affinity for the μ and δ receptors and lesser affinity for the κ receptor.[1] Buprenorphine, like fentanyl, has high lipid solubility, but has a lower intrinsic activity than fentanyl. Differences between buprenorphine and pure μ opioid agonists such as fentanyl, including relatively slow onset of action, prolonged duration of action, resistance to antagonism by naloxone, and lack of correlation between plasma concentrations and analgesic effects, have been explained by differences in the way buprenorphine binds to opioid receptors. In a study *in vitro* buprenorphine had slow rates of association and dissociation from the opioid receptor when compared with fentanyl.[2]

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Administration in children. Buprenorphine is used for the relief of moderate to severe **pain** in children. In the UK, those aged from 6 months to 12 years may be given 3 to 6 micrograms/kg by *intramuscular* or slow *intravenous* injection every 6 to 8 hours; up to 9 micrograms/kg may be given if required in refractory cases. In the USA, parenteral buprenorphine is licensed in children aged 2 years and over; usual doses of 2 to 6 micrograms/kg may be given intramuscularly or intravenously every 4 to 6 hours to those up to 12 years old. The *sublingual* route is licensed in the UK in children aged from 6 to 12 years and the following doses are given every 6 to 8 hours according to body-weight: 16 to 25 kg, 100 micrograms; 25 to 37.5 kg, 100 to 200 micrograms; 37.5 to 50 kg, 200 to 300 micrograms. Older children requiring pain relief may be given the usual adult dose (see above) for all the above routes.

Buprenorphine is also used in the treatment of **opioid dependence**; adolescents aged 16 years and over may be given the usual adult dose (see above).

Opioid dependence. Buprenorphine is used in the treatment of opioid dependence (p.101). Its agonist-antagonist properties may mean that it has a lower potential for dependence and a lower risk of respiratory depression in overdose than pure agonists such as methadone. Buprenorphine can be used as substitution therapy in patients with moderate opioid dependence for acute management of withdrawal and in maintenance treatment as an alternative to or together with methadone. However, in patients dependent on high doses of opioids buprenorphine may precipitate withdrawal due to its partial antagonist properties; the daily opioid dose should be reduced gradually in such patients before beginning buprenorphine. Abuse of the preparation, as with other substitution therapies, may be a problem. A combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries as a deterrent to abuse.

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Pain. ***ACUTE PAIN.*** The *BNF* considers that buprenorphine may antagonise the analgesic effect of other opioids and is generally not recommended for the management of *postoperative* pain. Nonetheless, it can be given intramuscularly, intravenously, or sublingually for this purpose, although the intravenous route may be preferred for acute pain relief. The epidural route[1] and continuous subcutaneous infusion[2] have also been used; an intranasal formulation of buprenorphine is under investigation for the management of postoperative pain.[1] Patient-controlled analgesia with intravenous[3] and intramuscular[4] buprenorphine has been effective although its long half-life may limit such use.

Buprenorphine had no adverse cardiovascular effects when given intravenously after open-heart surgery,[5] suggesting that it was a suitable analgesic for patients with unstable circulation. Epidural analgesia with buprenorphine has also been used after cardiac surgery.[6] Buprenorphine was also considered suitable for the relief of pain in *myocardial infarction*.[7]

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CHRONIC PAIN. Transdermal buprenorphine is used for chronic intractable cancer pain.[1-4] It has also been used successfully in chronic non-cancer pain including neuropathic pain;[1,2,4-6] however, licensed product information states that this route is not suitable for the treatment of acute pain.

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6. Hans G. Buprenorphine—a review of its role in neuropathic pain. *J Opioid Manag* 2007; **3:** 195–206.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Magnogen†; Temgesic†; ***Austral.:*** Norspan; Subutex; Temgesic; ***Austria:*** Subutex; Temgesic; Transtec; Tridol; ***Belg.:*** Subutex; Temgesic; Transtec; ***Braz.:*** Temgesic; ***Chile:*** Transtec; ***Cz.:*** Norspan; Suboxone; Subutex; Temgesic; Transtec; ***Denm.:*** Anorfin; Norspan; Subutex; Temgesic; Transtec; ***Fin.:*** Subutex; Temgesic; ***Fr.:*** Suboxone; Subutex; Temgesic; ***Ger.:*** Subutex; Temgesic; Transtec; ***Gr.:*** Subutex; ***Hong Kong:*** Subutex; Temgesic; ***Hung.:*** Bupren; Transtec; ***India:*** Norphin; Pentorel; Tidigesic†; ***Indon.:*** Subutex; ***Irl.:*** BuTrans; Temgesic; Transtec; ***Israel:*** Nopan; Subutex; ***Ital.:*** Subutex; Temgesic; Transtec; ***Malaysia:*** Suboxone; Subutex†; Temgesic†; ***Mex.:*** Brospina; Temgesic; Transtec; ***Neth.:*** Temgesic; ***Norw.:*** Subutex; Temgesic; ***NZ:*** Suboxone; Temgesic; ***Pol.:*** Bunondol; Transtec; ***Port.:*** Buprex; Norspan; Suboxone; Subutex; Transtec; ***Rus.:*** Nopan (Нопан)†; Transtec (Трансгек); ***S.Afr.:*** Subutex; Temgesic; ***Singapore:*** Subutex†; Temgesic†; ***Spain:*** Buprex; Prefin†; Subutex; Transtec; ***Swed.:*** Norspan; Subutex; Temgesic; ***Switz.:*** Subutex; Temgesic; Transtec; ***Thai.:*** Buprine; Temgesic†; ***UK:*** BuTrans; Suboxone; Subutex; Temgesic; Transtec; ***USA:*** Buprenex; Suboxone; Subutex.

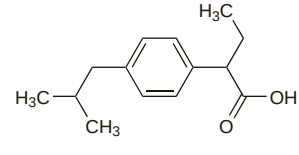
Butibufen Sodium *(rINNM)*

Butibufén sódico; Butibufène Sodique; FF-106 (butibufen); Natrii Butibufenum. Sodium 2-(4-isobutylphenyl)butyrate.

Натрий Бутибуфен

$C_{14}H_{19}NaO_2$ = 242.3.

CAS — 55837-18-8 (butibufen); 60682-24-8 (butibufen sodium).



(butibufen)

Profile

Butibufen sodium is an NSAID (p.96) that has been used orally in inflammatory and rheumatic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Mijal†.