Paracetamol *(BAN, rINN)*

Acetaminofeno; Acetaminophen; *N*-Acetyl-*p*-aminophenol; Asetaminofen; Paracétamol; Paracetamolis; Paracetamolum; Parasetamol; Parasetamoli. 4′-Hydroxyacetanilide; *N*-(4-Hydroxyphenyl)acetamide.

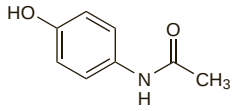
Парацетамол

$C_8H_9NO_2$ = 151.2.

CAS — 103-90-2.

ATC — N02BE01.

ATC Vet — QN02BE01.



NOTE. Compounded preparations of paracetamol may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—paracetamol and codeine phosphate
- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w)
- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol
- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol, respectively
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol
- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w)
- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

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

Ph. Eur. 6.2 (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 31 (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1*N* sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

Adverse Effects and Treatment

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, below.

◊ References.

1. Graham GG, *et al.* Tolerability of paracetamol. *Drug Safety* 2005; **28:** 227–40.

Effects on the kidneys. For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, p.98.

See also under Overdosage, below.

Effects on the respiratory tract. The results of a case-control study[1] have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, a further study and a review have found an increase in the prevalence of asthma[2,3] and COPD[2] with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, below). However, another review[4] stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdosage. The review concluded that a strong link between paracetamol use and asthma was unlikely.

1. Shaheen SO, *et al.* Frequent paracetamol use and asthma in adults. *Thorax* 2000; **55:** 266–70.
2. McKeever TM, *et al.* The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; **171:** 966–71.
3. Eneli I, *et al.* Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; **127:** 604–12.
4. Nuttall SL, *et al.* Does paracetamol cause asthma? *J Clin Pharm Ther* 2003; **28:** 251–7.

Hypersensitivity. Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults[1-4] and children.[5,6] Angioedema has also been reported.[7] Fixed drug eruptions, confirmed by rechallenge, have been described,[8-11] and toxic epidermal necrolysis has occurred.[12]

1. Stricker BHC, *et al.* Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; **291:** 938–9.
2. Van Diem L, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990; **38:** 389–90.
3. Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hosp Med* 1999; **60:** 66–7.
4. Bachmeyer C, *et al.* Acetaminophen (paracetamol)-induced anaphylactic shock. *South Med J* 2002; **95:** 759–60.
5. Ellis M, *et al.* Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* 1989; **114:** 654–6.
6. Bousetta K, *et al.* Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; **60:** 1174–7.
7. Idoko JA, *et al.* Angioneurotic oedema following ingestion of paracetamol. *Trans R Soc Trop Med Hyg* 1986; **80:** 175.
8. Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; **115:** 357–9.
9. Cohen HA, *et al.* Fixed drug eruption caused by acetaminophen. *Ann Pharmacother* 1992; **26:** 1596–7.
10. Harris A, Burge SM. Vasculitis in a fixed drug eruption due to paracetamol. *Br J Dermatol* 1995; **133:** 790–1.
11. Hern S, *et al.* Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; **139:** 1129–31.
12. Halevi A, *et al.* Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; **34:** 32–4.

Overdosage. Acute ***oral*** overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Ingestion of as little as 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Patients should be considered at risk of severe liver damage if they have ingested more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.[1,2]

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at special risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia or AIDS. It has also been suggested that fasting may predispose to hepatotoxicity.[3]

Early **signs** of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly. However, as both paracetamol[4] and acetylcysteine[5] can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.[6]

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)[2] in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

Treatment of oral paracetamol overdosage. The management of paracetamol overdosage as practised in the UK and US has been the subject of numerous reviews.[3,6-13] Guidelines have also been issued in the UK by the Paracetamol Information Centre.[14] Separate consensus guidelines have also been issued by clinical toxicologists in Australia and New Zealand.[15]

Prompt treatment is essential, even when there are no obvious symptoms, and all patients should be admitted to hospital; full supportive measures should also be instituted.

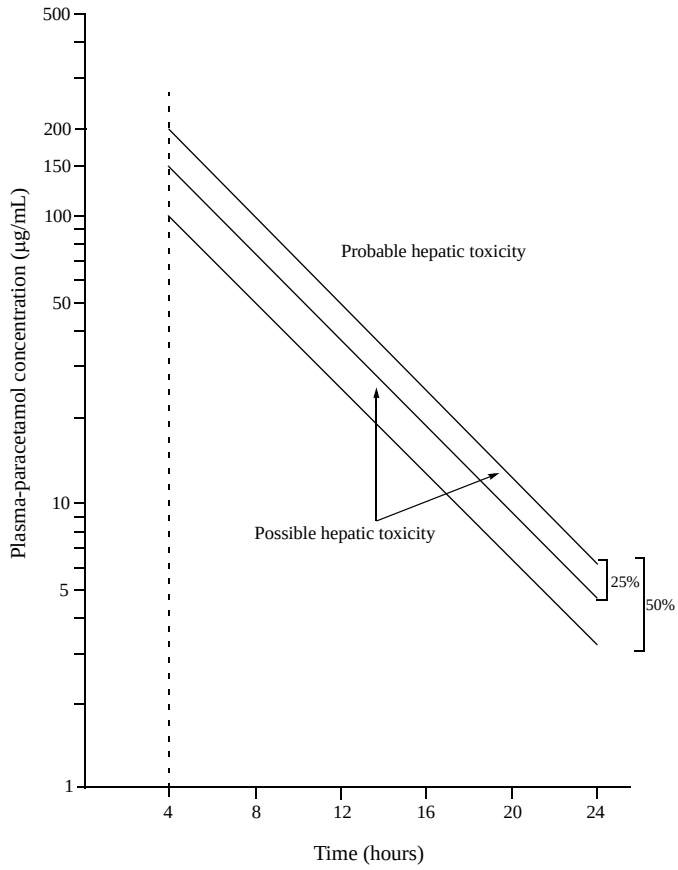
- Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.
- There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.
- The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 (p.109) and Figure 2 (p.109). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is higher than the appropriate line (but see below).
- Patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or those with malnutrition or a history of alcohol abuse, are considered at high risk, and should receive an antidote even if their plasma-paracetamol concentrations are up to 50% below the standard reference line.
- Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatic toxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.[16-18] Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.[19-21]
- Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.
- Deaths from liver failure have occurred in patients presenting with plasma-paracetamol concentrations below the treatment line: suggested explanations include inadequate patient histories and a need for a lower treatment threshold.[22]
- If there is any doubt about timing or the need to treat, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.[23]
- Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

Choice of antidote. Acetylcysteine (p.1548) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.[6,24] Intravenous use has been associated with anaphylactic reactions but is the preferred route in the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also used, and is clearly effective. The use of methionine (p.1450) by mouth is licensed in the UK, despite the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and may be used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting.

Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,[25] and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.[26,27] Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.[28]

- An initial dose of 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given intravenously over 15 minutes in the UK, or over 60 minutes in the USA. This is followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.

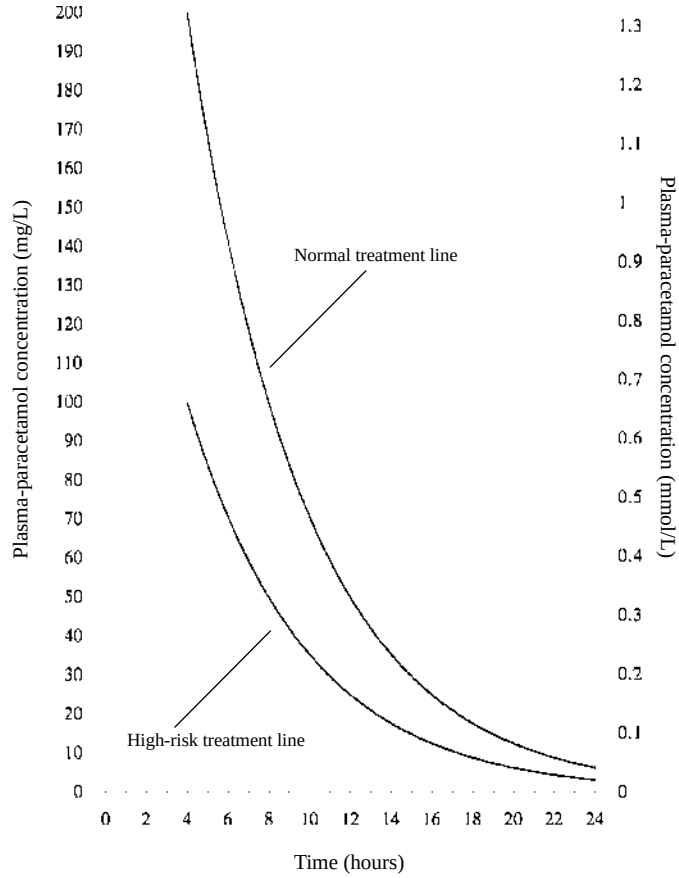
Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.



Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55:** 871–6.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. The solid line 25% below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose.
5. The solid line 50% below the standard nomogram is to assess the possible hepatic toxicity in patients receiving enzyme-inducing drugs or with malnutrition or a history of alcohol abuse.
6. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified release preparations of paracetamol.

Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.



Courtesy of P A Routledge.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. Patients whose plasma-paracetamol concentrations are above the normal treatment line should be treated.
5. Patients on enzyme-inducing drugs or with malnutrition or a history of alcohol abuse should be treated if their plasma-paracetamol concentrations are above the high-risk treatment line.
6. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified release preparations of paracetamol.

- In the USA, acetylcysteine may also be given orally as an alternative to parenteral treatment. It is given as an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Some[29] have suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas others[30] have found that the efficacy of acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol overdosage. However, it is not as effective if treatment is delayed[31-33] and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.

- The usual oral dose of methionine in adults and children over 6 years is 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children under 6 years should be given 1 g every 4 hours for 4 doses. It has also been given intravenously.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the doses quoted above refer to DL-methionine. Preparations containing both methionine and paracetamol (comethiamol) have been formulated for use in situations where overdosage may occur. However, the issue of whether methionine should be routinely added to paracetamol preparations is contentious for medical and ethical reasons.

Histamine H_2-antagonists. It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.[6,10,11,34]

Liver transplantation may be considered as a last recourse in some patients.

After maternal **overdosage during pregnancy** fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases.[35]

There is little information available on overdosage when paracetamol is given as an ***intravenous infusion***. The standard nomogram may not be appropriate in determining treatment from plasma-paracetamol concentrations after intravenous overdose, as it is based on data from acute paracetamol ingestion rather than intravenous administration. The National Poisons Information Service in the UK recommends that the need for antidote treatment should be based on the total administered dose of paracetamol and/or any resultant hepatic impairment.

1. Miles FK, *et al.* Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; **171:** 472–5.
2. American Academy of Pediatrics Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001; **108:** 1020–4.
3. Whitcomb DC, *et al.* Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* 1994; **272:** 1845–50.
4. Whyte IM, *et al.* Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. *Ther Drug Monit* 2000; **22:** 742–8.
5. Schmidt LE, *et al.* Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. *Lancet* 2002; **360:** 1151–2.
6. Brok J *et al.* Interventions for paracetamol (acetaminophen) overdoses. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/10/06).
7. Routledge P, *et al.* Paracetamol (acetaminophen) poisoning. *BMJ* 1998; **317:** 1609–10.
8. Makin AJ, *et al.* Management of severe cases of paracetamol overdosage. *Br J Hosp Med* 1994; **52:** 210–13.
9. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:** 547–52.
10. Prescott LF. Paracetamol overdose. In: *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996: 401–73.
11. Zed PJ, Krenzelok EP. Treatment of acetaminophen overdose. *Am J Health-Syst Pharm* 1999; **56:** 1081–91.
12. Kozer E, Koren G. Management of paracetamol overdose: current controversies. *Drug Safety* 2001; **24:** 503–12.

13. Dart RC, *et al.* Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006; **44:** 1–18.
14. Paracetamol Information Centre. *Guidelines for the management of acute paracetamol overdosage (revised 2007).* Also available at: http://www.pharmweb.net/pwmirror/pwy/paracetamol/chart.html (accessed 23/07/08)
15. Daly FF, *et al.* Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration: a consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. *Med J Aust* 2008; **188:** 296–301.
Also available at: http://www.mja.com.au/public/issues/188_05_030308/dal10916_fm.html (accessed 13/08/08)
16. Graudins A, *et al.* Overdose of extended-release acetaminophen. *N Engl J Med* 1995; **333:** 196.
17. Vassallo S, *et al.* Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity. *Ann Intern Med* 1996; **125:** 940.
18. Dart RC, *et al.* The safety profile of sustained release paracetamol during therapeutic use and following overdose. *Drug Safety* 2005; **28:** 1045–56.
19. Temple AR, Mrazik TJ. More on extended-release acetaminophen. *N Engl J Med* 1995; **333:** 1508.
20. Graudins A, *et al.* More on extended-release acetaminophen. *N Engl J Med* 1995; **333:** 1508–9.
21. Cetaruk EW, *et al.* Extended-release acetaminophen overdose. *JAMA* 1996; **275:** 686.
22. Bridger S, *et al.* Deaths from low dose paracetamol poisoning. *BMJ* 1998; **316:** 1724–5.
23. Aujla KS, *et al.* Nomogram does not show absolute concentration for treatment. *BMJ* 1998; **317:** 1655.
24. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; **63:** 1821–7.
25. Parker D, *et al.* Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990; **9:** 25–7.
26. Smilkstein MJ, *et al.* Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose: analysis of the National Multicenter Study (1976 to 1985). *N Engl J Med* 1988; **319:** 1557–62.
27. Harrison PM, *et al.* Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990; **335:** 1572–3.
28. Keays R, *et al.* Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991; **303:** 1026–9.
29. Chamberlain JM, *et al.* Use of activated charcoal in a simulated poisoning with acetaminophen: a new loading dose for N-acetylcysteine? *Ann Emerg Med* 1993; **22:** 1398–1402.
30. Spiller HA, *et al.* A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. *Ann Emerg Med* 1994; **23:** 519–23.
31. Vale JA, *et al.* Intravenous N-acetylcysteine: the treatment of choice in paracetamol poisoning? *BMJ* 1979; **2:** 1435–6.
32. Vale JA, *et al.* Treatment of acetaminophen poisoning: the use of oral methionine. *Arch Intern Med* 1981; **141:** 394–6.
33. Tee LGB, *et al.* N-Acetylcysteine for paracetamol overdose. *Lancet* 1986; **i:** 331–2.
34. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.
35. Wilkes JM, *et al.* Acetaminophen overdose in pregnancy. *South Med J* 2005; **98:** 1118–22.

Pancreatitis. Drug-induced pancreatitis associated with paracetamol was reported[1] to be a rare reaction only occurring in patients taking more than recommended doses. In a retrospective study of data from 814 patients who had taken paracetamol overdoses, hyperamylasaemia was detected in 246, and was more common and more severe in patients transferred to a specialist unit because of more severe poisoning.[2] However, acute pancreatitis was diagnosed only in 33 cases.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Schmidt LE, Dalhoff K. Hyperamylasaemia and acute pancreatitis in paracetamol poisoning. *Aliment Pharmacol Ther* 2004; **20:** 173–9.

Precautions

Paracetamol should be given with care to patients with impaired kidney or liver function. It should also be given with care to patients with alcohol dependence.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving paracetamol, 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 paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant.

Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/mL were achieved in 1 to 2 hours. Plasma concentrations were determined in 2 mothers; a breast milk/plasma ratio of about 1 was reported.[2] Similar findings have been reported from other studies.[3,4]

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 19/10/06)
2. Berlin CM, *et al.* Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatr Pharmacol* 1980; **1:** 135–41.
3. Hurden EL, *et al.* Excretion of paracetamol in human breast milk. *Arch Dis Child* 1980; **55:** 969–72.
4. Bitzén P-O, *et al.* Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 123–5.

Hepatic impairment. A short review[1] concluded that there was evidence that paracetamol could be and had been used safely in patients with liver disease. Studies had also shown that although the half-life of paracetamol was prolonged in such patients, glutathione concentrations in those taking recommended doses were not depleted to the critical levels that would enable accumulation of paracetamol's hepatotoxic metabolite. The *BNF* warns that large doses should be avoided.

1. Benson GD, *et al.* The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* 2005; **12:** 133–41.

Pregnancy. Paracetamol is generally considered to be the analgesic of choice in pregnant patients. However, the frequent use of paracetamol (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant[1] which may persist into childhood[2] (but see also Effects on the Respiratory Tract, above). The authors emphasised that the number of pregnant women taking frequent doses was very small and they recommended that *infrequent* paracetamol should remain the analgesic of choice in pregnancy.

1. Shaheen SO, *et al.* Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; **57:** 958–63.
2. Shaheen SO, *et al.* Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; **35:** 18–25.

Renal impairment. Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.[1-3] It has been suggested that paracetamol itself may be regenerated from these metabolites.[1,2] There are conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.[2,3]

1. Prescott LF, *et al.* Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. *Eur J Clin Pharmacol* 1989; **36:** 291–7.
2. Martin U, *et al.* The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. *Eur J Clin Pharmacol* 1991; **41:** 43–6.
3. Martin U, *et al.* The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. *Eur J Clin Pharmacol* 1993; **45:** 141–5.

Interactions

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

◊ Reviews.

1. Toes MJ, *et al.* Drug interactions with paracetamol. *Am J Ther* 2005; **12:** 56–66.

Antibacterials. The plasma-paracetamol concentrations considered an indication for antidote treatment (see under Overdosage, above) should be halved in patients receiving enzyme-inducing drugs such as *rifampicin*. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving *isoniazid*, alone[1-3] or with other drugs for tuberculosis.[4]

For the effects of paracetamol on *chloramphenicol*, see p.241.

1. Murphy R, *et al.* Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann Intern Med* 1990; **113:** 799–800.
2. Moulding TS, *et al.* Acetaminophen, isoniazid, and hepatic toxicity. *Ann Intern Med* 1991; **114:** 431.
3. Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993; **88:** 590–2.
4. Nolan CM, *et al.* Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. *Chest* 1994; **105:** 408–11.

Anticoagulants. For the effects of paracetamol on oral anticoagulants, see under Warfarin, p.1427.

Antiepileptics. The plasma-paracetamol concentrations considered an indication for antidote treatment (see under Overdosage, above) should be halved in patients receiving enzyme-inducing drugs such as *carbamazepine*, *phenobarbital*, *phenytoin*, or *primidone*.

For the effects of paracetamol on *lamotrigine*, see p.486.

Antivirals. For reports of adverse effects on the liver associated with use of paracetamol with antiviral drugs, see under Interferon Alfa, p.888 and Zidovudine, p.915.

Probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.[1] Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

1. Kamali F. The effect of probenecid on paracetamol metabolism and pharmacokinetics. *Eur J Clin Pharmacol* 1993; **45:** 551–3.

Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

◊ References.

1. van der Marel CD, *et al.* Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol* 2003; **59:** 243–51.

Absorption. The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subjects.[1]

1. Prescott LF, *et al.* Impaired absorption of paracetamol in vegetarians. *Br J Clin Pharmacol* 1993; **36:** 237–40.

Uses and Administration

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain and for fever (p.10). It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer, and children.

The usual **oral** dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may also be given as suppositories in a **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Paracetamol is also given by **intravenous** infusion over 15 minutes; dosage may be calculated by weight as follows:

- patients weighing over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
- from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less)

For doses in children or in renal impairment, see below.

◊ References.

1. Prescott LF. *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996.
2. Bannwarth B, Péhourcq F. Bases pharmacologiques de l'emploi du paracétamol: aspects pharmacocinétiques et pharmacodynamiques. *Drugs* 2003; **63** (suppl 2): 5–13.
3. Prescott LF. Nouvelles perspectives avec le paracétamol. *Drugs* 2003; **63** (suppl 2): 51–6.

Administration in children. In the UK, the licensed **oral** doses in children are:

- 3 months to 1 year: 60 to 120 mg
- 1 to 5 years: 120 to 250 mg
- 6 to 12 years: 250 to 500 mg

These doses may be given every 4 to 6 hours when necessary up to a maximum of 4 doses in 24 hours.

In younger children the *BNFC* suggests the following doses:

- neonates 28 to 32 weeks postmenstrual age (gestational age at birth plus chronological age): 20 mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 20 mg/kg as a single dose then 10 to 15 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher doses for use in children with more ***severe*** symptoms:

- 1 to 3 months: 20 mg/kg as a single dose followed by 15 to 20 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- older children: 20 mg/kg every 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer if necessary followed by 15 mg/kg every 6 hours. Usual adult maximum doses (see above) should not be exceeded

For ***post-immunisation pyrexia***, a dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after six hours; if the pyrexia persists after that dose, medical advice should be sought.

UK licensed **rectal** doses, which may be given to children every 4 to 6 hours, up to 4 times daily are:

- 1 to 5 years: 125 to 250 mg
- 6 to 12 years: 250 to 500 mg

The *BNFC* suggests the following rectal doses in younger children:

- neonates 28 to 32 weeks postmenstrual age: 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours
- 3 to 12 months of age: 60 to 125 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours

The *BNFC* also suggests higher rectal doses for use in children with more ***severe*** symptoms:

- 1 to 3 months: 30 mg/kg as a single dose followed by 20 mg/kg every 8 hours to a maximum of 60 mg/kg daily
- older children: 40 mg/kg as a single dose followed by 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer, if necessary, before reducing to 15 mg/kg every 6 hours. Usual adult maximum doses (see above) should not be exceeded

Doses by **intravenous** infusion in children, given over 15 minutes, are:

- full-term neonates and other children below 10 kg: single doses of 7.5 mg/kg every 4 or more hours, to a maximum of 30 mg/kg daily; intravenous paracetamol has not been studied in premature neonates
- between 10 and 33 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 2 g daily (whichever is less)
- from 33 to 50 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less)
- over 50 kg: usual adult doses (see above)

The intravenous solution may be diluted to a minimum strength of one-tenth of its original concentration in sodium chloride 0.9% or glucose 5%; the diluted solution should be used within 1 hour of preparation.

It has been suggested[1] that the recommended doses of paracetamol for children may result in subtherapeutic blood concentrations, and that an initial loading dose should be given, followed by regular doses up to the recommended maximum daily dose. However, the appropriate maximum daily dose remains controversial, and there is obvious concern given the risks of overdosage.

1. Zacharias M, Watts D. Pain relief in children. *BMJ* 1998; **316:** 1552.

Administration in renal impairment. In patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

Headache. Non-opioid analgesics such as paracetamol, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine (see p.616) and tension-type headache (see p.617). These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

Pain. Paracetamol is used in the management of mild to moderate pain (see Choice of Analgesic, p.2). It is of similar potency to aspirin, but with weak anti-inflammatory activity. Paracetamol may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5). Paracetamol is the preferred choice for pain in children (p.3) because of the association of aspirin with Reye's syndrome in this age group (see p.22). In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of paracetamol. However, it may be of benefit for simple pain control in rheumatoid arthritis (p.11) and ankylosing spondylitis (see under Spondyloarthropathies, p.13), although these patients usually require the additional anti-inflammatory effects provided by NSAIDs. Synovial inflammation is usually only a minor component of osteoarthritis (p.11), and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. Paracetamol is useful for the relief of acute low back pain (p.7).

Dependence and tolerance are not a problem with non-opioid analgesics such as paracetamol, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

Preparations

BP 2008: Co-codamol Capsules; Co-codamol Tablets; Co-dydramol Tablets; Co-proxamol Tablets; Dispersible Paracetamol Tablets; Effervescent Co-codamol Tablets; Paediatric Paracetamol Oral Solution; Paracetamol Capsules; Paracetamol Oral Suspension; Paracetamol Suppositories; Paracetamol Tablets; Soluble Paracetamol Tablets;

USP 31: Acetaminophen and Aspirin Tablets; Acetaminophen and Caffeine Tablets; Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen Capsules; Acetaminophen Extended-Release Tablets; Acetaminophen for Effervescent Oral Solution; Acetaminophen Oral Solution; Acetaminophen Oral Suspension; Acetaminophen Suppositories; Acetaminophen Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Hydrocodone Bitartrate and Acetaminophen Tablets; Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules; Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Napsylate and Acetaminophen Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acetolit; Alikal Dolor; Apracur Antifebril; Bio Grip-T; Causalon; Custodial†; Dirox; Doxidol; Distancito†; Fiebrol†; Fiebrolito; Flash; Guemusin†; Inmunogrip T Caliente; Invernosan†; Itedal; Mejoral; Multifebrin†; Nodipir; Nodolex†; Novo Asat; Para Z Mol†; Parageniol; Paratral; Parclen; PH 4 Plus†; Plovacal; Predualito†; Qura Plus; Tafirol; Termofren; Tetradox; Tylenol†; Vick Vitapyrena; Viclor; ***Austral.:*** Chemists Own Pain & Fever; Childrens Panadol; Dymadon; Febridol; Lemsip; Ordov Febrigesic†; Panadol; Panamax; Parahexal; Paralgin; Perfalgan; Setamol†; Tylenol†; ***Austria:*** Becetamol; Ben-u-ron; Duaneo; Enelfa; Gewamol; Grippostad; Kratofin simplex; Mexalen; Momentum; OSA; Parakapton; Paraspeed; Peinfort; Perfalgan; ***Belg.:*** Algostase Mono; Curpol; Dafalgan; Dolol-Instant; Dolprone; Lemsip; Panadol; Pe-Tam; Perdolan; Perfusalgan; Sanicopyrine; ***Braz.:*** Acetamil; Acetofen; Anatyl; Cefabrina; Cetafrin†; Cetynol†; Contradol†; Cyfenol; Dorfen; Dorib†; Dorico; Dorsanol; Dorvan†; Emsgrip; Febralgin†; Fervex; Gripeonil†; Gripotermon; Pacemol†; Paracemil†; Paracen; Paralgen; Paratermol†; Piramin; Pyrimel; Sonridor; Termo-Ped†; Termol; Tilekin; Trifen; Tyflen†; Tylalgin†; Tyleflan†; Tylenol; Tylephen; Tylidol; Unigrip; ***Canad.:*** Abenol; Acet; Alsiphene†; Artritol; Atasol; Cephanol; Childrens Feverhalt; Multi-gesic; Novo-Gesic; Pain Aid Free; Panadol; Pediatrix; Robigesic†; Tantaphen; Tempra; Tylenol; ***Chile:*** Acamol; Asafen Nueva Formula†; Cotibin Compuesto; Cryogenine Plus†; Daimeton†; Fibrimol†; Geniol-P; Kitadol; Panadol; Panagesic; Parox Meltab; Rapidol; Supracalm; Tapsin Infantil; Tapsin SC; Winasorb; Xumadol; Zolben; ***Cz.:*** Ben-u-ron; Calpol; Daleron; Effect Comfort; Efferalgan; Gelocatil†; Medipyrin; Mexalen; Panadol; Paralen; Paramax Rapid; Perfalgan; ***Denm.:*** Pamol; Panam; Panodil; Paratabs; Perfalgan; Pinex; ***Fin.:*** Pamol; Panadol; Para-Suppo; Para-Tabs; Paraceon; Paramax Rap; Perfalgan; ***Fr.:*** Claradol; Dafalgan; Doliactic; Doliprane; Dolitabs; Dolko; Dolotec; Efferalgan; Efferalganodis; Expandox; Febrectol†; Geluprane; Panadol; Paralyoc; Perfalgan; ***Ger.:*** Ben-u-ron; Captin; Contac Erkaltungs-Trunk; Doloreduct†; Dorocoff-Paracetamol†; Enelfa; Fensum; Grippostad Heisstrank†; Mono Praecimed; Paedialgon; Parapaed; PCM; Perfalgan; Pyromed†; RubieMol†; Sinpro N; Togal; ***Gr.:*** Apotel; Calmodor; Cetinject†; Dalminette†; Depon; Depon Maximum; Depon Odis; Dolal; Genspir†; Lonarid Aplo; Panadol; Par; Perfalgan; protAlgon; Tunelzin†; ***Hong Kong:*** Afebrin†; Angenol; Arfen; Ben-u-ron; Biogesic; Calpol†; Children's Tylenol†; Christamol; Cortal for Children; Dhamol; Europain; Fortolin†; Infant's Tylenol†; Junior Strength Tylenol†; Panadol; Parcemol; Parmol; Progesic; Serimol; Setamol; Tiffy; Tylenol†; Uni-Febrin; ***Hung.:*** Ben-u-ron; Efferalgan; Febrilin; Grippostad; Mexalen; Panadol; Paramax Rapid; Perfalgan; Rubophen; ***India:*** Calpol; Crocin; Disprin Paracetamol; Doliprane†; Febridol; Febrinil; Jagcin; Malidens; Pacimol; Paracin; Paracip; Parafizz†; Pyrexon; Pyrigesic; Ultragin; ***Indon.:*** Afebrin; Alphamol; Biogesic; Bodrex Forte; Calapol; Contratemp; Cupanol; Dapyrin; Dumin; Erphamol; Farmadol; Fevrin; Grafadon; Gunaceta; Itamol; Lanamol; Maganol; Naprex; Nasamol; Nufadol; Ottopan; Pamol; Panadol; Paracetol; Praxion; Progesic; Propyretic; Pyrex; Pyrexin; Pyridol; Sanmol; Sumagesic; Tempra; Termorex; Turpan; Xepamol; ***Irl.:*** Anadin Paracetamol; Calpol; Disprol; Hedex; Lemsip Children's Cold Relief; Panadol; Paralief; Paralink; Parapaed; Paratabs; Perfalgan; Tylenol†; ***Israel:*** Abrol; Abrolet; Acamol; Acamoli; Aldolor; Dexamol; Dexamol Kid; Efferalgan†; Panadol; Paramol; Paramolan; Rokamol; Sensamol; Supramol†; Vimoli; ***Ital.:*** Acetamol; Efferalgan; Levadol; Minofen; Normaflu†; Panadol; Perfalgan; Piros; Puemol†; Sanipirina; Tachipirina; ***Malaysia:*** Acet†; Arfen; Biogesic; Dhamol; Dumin†; Hoemal; Naprex†; Panadol; Parafizz; Partamol; Poro; Rapidol; Serimol†; Setromol†; Uphamol; ***Mex.:*** Abatem; Ac-Fast; Acetafen; Acetif; Alpirex; Amolgen; Analphen; Andopan†; Andox; Antidol; Biofer; Bremotel†; Calinofen; Coriver; Datril; Dismifen; Dolgan Flash; Dolotemp†; Doluvital; Dolviran; Farpik; Febran†; Ferridal; Filanc; Frilen; Ginol†; Icetazol; Ifutemp†; Infalgina; Magnidol; Magnidol-Plus; Mejoral Acti-Rapido; Mejoralito; Minofen; Neodol; Neodolito†; Nordinet Infantil; Notem; Panofen; Pharmacen; Piralgina; Piralgina 650; Piralyn; Piremol; Precifen; Prosedal; Quitadol; Resfin; Sedalito; Sinedol; Soltadol; Sons Piral; Sudis; Tafirol; Temperal; Tempire; Tempofin; Tempra; Tempre†; Temprin; Temzzard; Termotrin†; Tylenol; Tylex; Ulpafie; Winasorb; ***Neth.:*** Daro; Democyl; Finimal Junior†; Hedex; Kinder Finimal†; Lagalgin†; Momentum; Panadol; Perfalgan; Sinaspril-Paracetamol; Tylenol; Vicks Paracetamol; ***Norw.:*** Pamol; Panodil; Paracet; Perfalgan; Pinex; ***NZ:*** Disprol†; Lemsip Cold & Flu Original, Cold & Flu Max; Pacimol; Pamol; Panadol; Paracare; Parapaed; Perfalgan; ***Philipp.:*** Acet; Acetadol; Aeknil; Alvedon; Baropyrine; Biogesic; Calpol; Cloxina; Corgic; Crocin; Detramol; Dolexpel; Febrinil; Gendol; Gifaril P; Lexalgin; Medgenol; Naprex; Nektol; Neo-Kiddielets; Opigesic; Para-4-Kids; Parvid; Rexidol; Riber; Saridon; Tempain; Tempra; Tylenol; Ultragesic; Zestagesic; Zydinol; ***Pol.:*** Acenol; Apap; Calpol; Codipar; Efferalgan; Grippostad; Novo-Gesic; Panadol; Perfalgan; Tazamol; ***Port.:*** Anti-Gripe Asclepius; Atralidon; Beluron; Ben-u-ron; Calpol†; Cofedron; Dafalgan; Efferalgan; Fludeten†; Gelocatil; Katagrip; Neogrip; Panadol; Panasorbe; Pantadolor; Paracetol; Paramolan; Parsel; Perdolan Mono†; Perfalgan; Singrips; Supofen; Takiprina; Tylenol; Zaramol†; ***Rus.:*** Calpol (Калпол); Cefecon D (Цефекон Д); Daleron (Далерон); Dolomol (Доломол); Flutabs (Флюта6с); Panadol (Панадол); Perfalgan (Перфалган); ***S.Afr.:*** Anadin-3; Antalgic; Brunomol†; Calpol; Dolorol; Empaped; Fevamol; Go-Pain P; Junior Disprin†; Medpramol; Merck-Gesic†; Micro-Gesic; Napamol; Pacimol; Painamol; Panado; Paradco; Paramed; Perfalgan; Prolief; Pyradol; Tylenol; Varipan; Winpain†; ***Singapore:*** Acet; Biogesic; Calpol; Childrens Panadol Drops for Infants; Dhamol; Fibrexin; Milidon†; Napa; Naprex; Pacemol†; Panadol; Panamol; Paximol; Poro; Rapidol; Remedol; Tylenol; ***Spain:*** Acertol; Actron†; Antidol; Apiretal; Bandol†; Bolidol; Calmanticold†; Cupanol; Dafalgan; Dolgesic; Dolostop; Duorol; Efetamol; Efferalgan; Febrectal; Gelocatil; Melabon Infantil; Panadol; Parafludeten; Pediapirin†; Perfalgan; Resakal†; Resolvebohm; Sinmol; Talgo; Temperal†; Termalgin; Termocatil; Tylenol; Xumadol; ***Swed.:*** Alvedon; Curadon; Panodil; Perfalgan; Reliv; ***Switz.:*** Acetalgine; Becetamol; Ben-u-ron; Contre-Douleurs P; Dafalgan; Democyl†; Demogripal†; DoloStop nouvelle formule†; Dolprone; Influbene N; Kafa; Malex; Nina†; Osa Suppositoires contre douleurs et fievre; Panadol; Perfalgan; Pharmacard Family Douleurs & Fievre†; Rivodol†; Seranex N; Siniphen Nouvelle formule; Treupel Dolo Paracetamol; Treuphadol; Tylenol; Zolben; ***Thai.:*** A-Mol; Aceta-P†; Acetasil; Algogen; Biogesic; Calpol; Cemol; Daga; Denamol; Depyret; Detamol†; Fenn; Icolid Plus; Kit; Lotemp; Mypara; Nasa; Nutamol†; Panadol; Para GDEK; Para-G; Paracap; Paracet; Paragin; Paramol; Paramol TP; Paranal-L; Paranal†; Parat; Paratol; Partamol; Pemol; Pyracon; Pyretal†; Ramol; Sara†; Tempra; Tumdi; Tylenol; Tymol; Umeda Para-J; Unicap; Unimol; Uracet; Vemol†; Xebramol; ***Turk.:*** A-Per; Asomal; Babinoks; Berko-Setamol; Calpol; Efferalgan; Efpa; Ekosetol; Geralgine; Gripin; Minafen; Minoset; Noral; Panadol; Para-Nox; Paracet; Parasedol; Parol; Paroma; Pirofen; Polmofen; Sedalon; Setamol; Tamol; Tempo; Termacet; Termalgine; Tylol; Vermidon; Volpan; ***UAE:*** Adol; ***UK:*** Abdine Cold Relief; Alvedon; Anadin Paracetamol; Boots Pain Relief Suspension 6 Years Plus; Calpol; Disprol; Fennings Childrens Cooling Powders; Galpamol; Hedex; Infadrops; Mandanol; Medinol; Miradol; Obimol; Paldesic; Panadol; Panaleve; Paracets; Paraclear; Parapaed; Perfalgan; Salzone; ***USA:*** Acephen; Aceta; Apacet; Apap; Apra; Arthritis Pain Formula Aspirin Free; Aspirin Free Anacin; Aspirin Free Pain Relief; Bromo Seltzer; Childrens Dynafed Jr†; Childrens Mapap; Comtrex Maximum Strength Sore Throat; Dolono; Dynafed EX†; Feverall; Genapap; Genebs; Halenol; Infantaire; Liquiprin; Mapap; Maranox; Meda†; Oraphen-PD; Panadol; Panitone; Redutemp; Ridenol; Silapap; Tapanol†; Tempra; Tylenol; Tylenol Sore Throat Daytime; UN-Aspirin; Uni-Ace; ***Venez.:*** Acetafen; Acetalis; Aceval; Agurin; Alivax; Amifen; Ananty; Apiret; Apyrene; Atamel; Brexin; Cadafen†; Colprin†; Menpirin†; Paracor; Parstelin†; Tachipirin; Tempra; Tylenol; Tylex; Vestax; Winadol†.

Multi-ingredient: numerous preparations are listed in Part 3.

Parecoxib Sodium *(BANM, USAN, rINNM)*

Natrii Parecoxibum; Parecoxib sódico; Parécoxib Sodique; SC-69124A. *N*-{[*p*-(5-Methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl}-propionamide sodium.

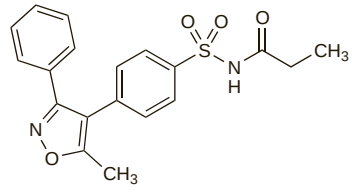
Натрий Парекоксиб

$C_{19}H_{17}N_2NaO_4S$ = 392.4.

CAS — 198470-84-7 (parecoxib); 197502-82-2 (parecoxib sodium).

ATC — M01AH04.

ATC Vet — QM01AH04.



(parecoxib)

Incompatibility. Parecoxib sodium should not be mixed with products other than those recommended in licensed product information (see Uses and Administration, below). In particular, the use of lactated Ringer's solution with or without glucose will cause parecoxib to precipitate. Parecoxib should also not be given in the same syringe as opioids. The use of sterile water for injection is not recommended as the resulting solution is not isotonic.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Hypersensitivity reactions, including anaphylaxis and angioedema and serious skin reactions, have been reported with valdecoxib and may therefore occur with parecoxib, a prodrug of valdecoxib (see also p.132). Parecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions occurred in patients with a history of allergic reactions to sulfonamides and the use of parecoxib is contra-indicated in such patients.

Parecoxib should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more), inflammatory bowel disease, and moderate to severe heart failure (NYHA class II to IV). It should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should also not be used after coronary artery bypass graft surgery as there may be an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, stroke, renal impairment, deep surgical infections, and sternal wound complications. This may apply especially in obese patients or those with a history of cerebrovascular disease. Parecoxib should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Caution is also recommended when using parecoxib in dehydrated patients; rehydration may be advisable before giving parecoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the general worldwide withdrawal of rofecoxib (see p.121). The short-term use of