Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Sufentanil). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Sufentanil Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de sufentanilo; R-33800; Sufentaniilisitraatti; Sufentanil citrát; Sufentanil, citrate de; Sufentanil Sitrat; Sufentanilcitrat; Sufentanili citras; Sufentanilio citratas; Szufentanil-citrát. *N*-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide citrate.

Суфентанила Цитрат

$C_{22}H_{30}N_2O_2S,C_6H_8O_7$ = 578.7.
CAS — 60561-17-3.
ATC — N01AH03.
ATC Vet — QN01AH03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Sufentanil Citrate). A white or almost white powder. Soluble in water and in alcohol; freely soluble in methyl alcohol. Protect from light.
USP 31 (Sufentanil Citrate). A white powder. Soluble in water; sparingly soluble in alcohol, in acetone, and in chloroform; freely soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Sufentanil (as the citrate) diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.[1]

1. Chapalain-Pargarde S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102 and Fentanyl, p.56.

Breast feeding. Concentrations of sufentanil were similar in colostrum and serum in 7 women given sufentanil by continuous epidural infusion during the first postoperative day after caesarean section. In the light of its poor oral availability such an amount was not considered to be a hazard to the breast-fed infant, and a maternal dose of 5 micrograms/hour epidurally was considered to be safe for such infants.[1]

1. Ausseur A, *et al.* Continuous epidural infusion of sufentanil after caesarean section: concentration in breast milk. *Br J Anaesth* 1994; **72** (suppl 1): 106.

Effects on the cardiovascular system. For a reference to the effects of sufentanil on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on the nervous system. There have been reports of tonic-clonic movements or seizures in a few patients receiving sufentanil.[1] There was no evidence of cortical seizure activity in a patient whose EEG was recorded,[2] suggesting that the observed myoclonus was not a convulsion or seizure.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Bowdle TA. Myoclonus following sufentanil without EEG seizure activity. *Anesthesiology* 1987; **67:** 593–5.

Effects on the respiratory system. Sufentanil, like other opioid agonists, causes dose-related respiratory depression. There have been reports of significant respiratory depression associated with chest wall rigidity in the early postoperative period after anaesthesia with intravenous sufentanil.[1,2] Respiratory depression has also been reported after intrathecal sufentanil for postoperative analgesia[3] and labour pain.[4]. A retrospective chart review[3] of a 6-year period, during which 4870 patients received intrathecal sufentanil for the management of labour pain, found that the case above was the only one of respiratory arrest reported in the group.

1. Goldberg M, *et al.* Postoperative rigidity following sufentanil administration. *Anesthesiology* 1985; **63:** 199–201.
2. Chang J, Fish KJ. Acute respiratory arrest and rigidity after anesthesia with sufentanil: a case report. *Anesthesiology* 1985; **63:** 710–11.
3. Fournier R, *et al.* Respiratory depression after 5 μgrams of intrathecal sufentanil. *Anesth Analg* 1998; **87:** 1377–8.
4. Ferouz F, *et al.* Risk of respiratory arrest after intrathecal sufentanil. *Anesth Analg* 1997; **85:** 1088–90.

The elderly. The pharmacokinetics of sufentanil in elderly patients have been variable in different studies, but a review[1] considered that there had been no evidence overall for differences between the elderly and younger adults. Nevertheless, as with fentanyl, reduced initial doses have been advised in the elderly.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.

Handling. Avoid contact with skin and the inhalation of particles of sufentanil citrate.

Obesity. The elimination half-life and volume of distribution of sufentanil were increased in obese subjects.[1,2] Licensed product information recommends that for obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of the patients' lean body-weight.

1. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in the obese. *Anesthesiology* 1986; **65** (suppl 3A): A562.
2. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in obese patients. *Anesth Analg* 1991; **73:** 790–3.

Interactions

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

Benzodiazepines. For the effects of using opioids such as sufentanil with benzodiazepines, see Analgesics under Interactions of Diazepam, p.989.

Pharmacokinetics

After parenteral doses sufentanil citrate has a rapid onset and short duration of action. The terminal elimination half-life of sufentanil is about 2.5 hours. It is extensively bound to plasma proteins (about 90%). It is metabolised in the liver and small intestine by *N*-dealkylation and *O*-demethylation and the inactive metabolites are excreted in the urine and faeces. About 80% of a dose is excreted within 24 hours and 2% is eliminated as unchanged drug. Sufentanil crosses the placenta and is distributed into breast milk.

◊ The pharmacokinetics of sufentanil have been reviewed.[1,2] Sufentanil is very lipid-soluble. Like alfentanil it is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. The elimination half-life lies between that of alfentanil and fentanyl. The manufacturers of sufentanil have given values for a three-compartment pharmacokinetic model with a distribution half-life of 1.4 minutes, a redistribution half-life of 17.1 minutes, and an elimination half-life of 164 minutes. Accumulation may be relatively limited when compared with fentanyl. In practice the pharmacokinetics of sufentanil may vary according to the age and condition of the patient and the procedures undertaken. For example, the elimination half-life of sufentanil has been reported to be longer in patients undergoing cardiac surgery (595 minutes),[3] in hyperventilated patients (232 minutes),[4] in those undergoing abdominal aortic surgery (more than 12 hours),[5] and in ventilated intensive care patients under sedation (25.5 hours).[6]

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Howie MB, *et al.* Serum concentrations of sufentanil and fentanyl in the post-operative course in cardiac surgery patients. *Anesthesiology* 1984; **61:** A131.
4. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. *Br J Anaesth* 1989; **63:** 385–8.
5. Hudson RJ, *et al.* Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; **70:** 426–31.
6. Ethuin F, *et al.* Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med* 2003; **29:** 1916–20.

Administration. References to the pharmacokinetics of sufentanil given epidurally,[1,2] intrathecally,[1] or transdermally.[3]

1. Ionescu TI, *et al.* Pharmacokinetic study of extradural and intrathecal sufentanil anaesthesia for major surgery. *Br J Anaesth* 1991; **66:** 458–64.
2. Hansdottir V, *et al.* The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. *Anesth Analg* 1995; **80:** 724–9.
3. Sebel PS, *et al.* Transdermal absorption of fentanyl and sufentanil in man. *Eur J Clin Pharmacol* 1987; **32:** 529–31.

Children. Neonates (up to 1 month old) had a significantly lower plasma clearance rate and greater elimination half-life than infants (1 month to 2 years), children, and adolescents.[1] Others[2] have found that infants and small children (1 month to 3 years) with cardiac disease had higher clearance rates and shorter elimination half-lives than reported for adults. Older children (aged 2 to 8 years) with no history of cardiac, renal, or hepatic disease have also been noted to have shorter elimination half-lives and higher clearance rates than adults.[3]

1. Greeley WJ, *et al.* Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987; **66:** 1067–72.
2. Davis PJ, *et al.* Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. *Anesth Analg* 1987; **66:** 203–8.
3. Guay J, *et al.* Pharmacokinetics of sufentanil in normal children. *Can J Anaesth* 1992; **39:** 14–20.

Hepatic impairment. Because of the efficient hepatic extraction and clearance of sufentanil[1] liver dysfunction might be expected to affect its pharmacokinetics. However, elimination kinetics and plasma protein binding were found to be similar in cirrhotic and non-cirrhotic patients after a single dose of sufentanil.[2]

1. Schedewie H, *et al.* Sufentanil and fentanyl hepatic extraction rate and clearance in obese patients undergoing gastroplasty. *Clin Pharmacol Ther* 1988; **43:** 132.
2. Chauvin M, *et al.* Sufentanil pharmacokinetics in patients with cirrhosis. *Anesth Analg* 1989; **68:** 1–4.

Renal impairment. The pharmacokinetics of sufentanil were reported[1] to be unaffected in patients with chronic renal failure, although elevated plasma concentrations of sufentanil have been noted[2] in one such patient.

1. Sear JW. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *Br J Anaesth* 1989; **63:** 60–7.
2. Wiggum DC, *et al.* Postoperative respiratory depression and elevated sufentanil levels in a patient with chronic renal failure. *Anesthesiology* 1985; **63:** 708–10.

Uses and Administration

Sufentanil, a phenylpiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is highly lipid-soluble and more potent than fentanyl. Sufentanil is used as an analgesic adjunct in anaesthesia and as a primary anaesthetic in procedures requiring assisted ventilation. It has a rapid onset and recovery is considered to be more rapid than with fentanyl. It is also used as an analgesic in the management of postoperative pain and labour pain.

Sufentanil is given as the citrate either intravenously by slow injection or as an infusion, or epidurally. Doses are expressed as the base; sufentanil citrate 15 micrograms is equivalent to about 10 micrograms of sufentanil. Lower initial doses are advised in the elderly and debilitated patients. For obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of the patient's lean body-weight. For details of doses in children, see below. In all patients supplementary maintenance doses should be based on individual response and length of procedure. Doses of up to the equivalent of 8 micrograms/kg of sufentanil produce profound analgesia. Higher doses produce a deep level of anaesthesia but are associated with prolonged respiratory depression and assisted ventilation may be required in the postoperative period.

When used as an analgesic **adjunct to anaesthesia** with nitrous oxide and oxygen for surgical procedures lasting up to 8 hours, the total *intravenous* dosage should not exceed 1 microgram/kg per hour. It is customary to give up to 75% of the dose before intubation followed as necessary during surgery by additional injections of 10 to 50 micrograms or by a suitable continuous or intermittent infusion given so that the total hourly dose is not exceeded. Thus, for an operation lasting 1 to 2 hours the total dose would be 1 to 2 micrograms/kg with 0.75 to 1.5 micrograms/kg being given before intubation.

When used as a **primary anaesthetic** in major surgery *intravenous* doses of 8 to 30 micrograms/kg are given with 100% oxygen; doses of 25 to 30 micrograms/kg block sympathetic response including catecholamine release and are indicated in procedures such as cardiovascular surgery or neurosurgery. Anaesthesia may be maintained by additional injections of 0.5 to 10 micrograms/kg or by a suitable continuous or intermittent infusion given so that the total dosage for the procedure does not exceed 30 micrograms/kg.

In postoperative **pain**, sufentanil is given *epidurally* in an initial dose of 30 to 60 micrograms, which should provide analgesia for 4 to 6 hours. Additional boluses of up to 25 micrograms may be given at intervals of not less than 1 hour if necessary.

Sufentanil is also given *epidurally* for the relief of pain during labour and delivery. Recommended doses are 10 to 15 micrograms given with 10 mL of bupivacaine 0.125% (or its equivalent) with or without adrenaline;

the dose may be repeated twice at not less than one-hour intervals until delivery. The total dose of sufentanil should not exceed 30 micrograms.

◊ General reviews of sufentanil.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clin Pharm* 1991; **10:** 581–93.

Administration. Sufentanil is usually given intravenously, but the epidural route is also used (see below). Intranasal (see Anaesthesia, Pain, and Sedation, below), intrathecal (see below), and sublingual use (see Pain, below) have also been tried.

EPIDURAL. In a laboratory assessment of epidural sufentanil in healthy subjects,[1] a dose of 50 micrograms produced analgesia for 2 to 3 hours; analgesia was intensified and prolonged, and respiratory and other adverse effects, especially drowsiness, were reduced by the addition of adrenaline. Epidural sufentanil or fentanyl provided effective postoperative analgesia following caesarean section with comparable adverse effect profiles.[2] Sufentanil doses of 20 and 30 micrograms showed equivalent efficacy and provided greater analgesia for a longer duration than a dose of 10 micrograms. Addition of sufentanil to local anaesthetics such as bupivacaine during labour has considerably reduced the local anaesthetic requirements[3] and improved the quality of epidural analgesia.[4] Combination of sufentanil with a local anaesthetic (ropivacaine or bupivacaine) has been used for patient-controlled epidural analgesia (PCEA),[5-9] although an early study suggested that PCEA with sufentanil alone had little advantage over patient-controlled analgesia with intravenous morphine.[10]

Effective analgesia has been achieved in children with epidural sufentanil.[11]

1. Klepper ID, *et al.* Analgesic and respiratory effects of extradural sufentanil in volunteers and the influence of adrenaline as an adjuvant. *Br J Anaesth* 1987; **59:** 1147–56.
2. Grass JA, *et al.* A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
3. Buyse I, *et al.* Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. *Int J Obstet Anesth* 2007; **16:** 22–8.
4. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
5. Gogarten W, *et al.* A multicentre trial comparing different concentrations of ropivacaine plus sufentanil with bupivacaine plus sufentanil for patient-controlled epidural analgesia in labour. *Eur J Anaesthesiol* 2004; **21:** 38–45.
6. Boselli E, *et al.* Background infusion is not beneficial during labor patient-controlled analgesia with 0.1% ropivacaine plus 0.5 microg/ml sufentanil. *Anesthesiology* 2004; **100:** 968–72.
7. Bremerich DH, *et al.* Comparison of continuous background infusion plus demand dose and demand-only parturient-controlled epidural analgesia (PCEA) using ropivacaine combined with sufentanil for labor and delivery. *Int J Obstet Anesth* 2005; **14:** 114–20.
8. Missant C, *et al.* Patient-controlled epidural analgesia following combined spinal-epidural analgesia in labour: the effects of adding a continuous epidural infusion. *Anaesth Intensive Care* 2005; **33:** 452–6.
9. Schenk MR, *et al.* Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. *Anesth Analg* 2006; **103:** 1311–17.
10. Grass JA, *et al.* Patient-controlled analgesia after cesarean delivery: epidural sufentanil versus intravenous morphine. *Reg Anesth* 1994; **19:** 90–7.
11. Benlabed M, *et al.* Analgesia and ventilatory response to CO following epidural sufentanil in children. *Anesthesiology* 1987; **67:** 948–51.

INTRATHECAL. Sufentanil, alone or in combination, has been given intrathecally for labour pain: a combination of sufentanil, bupivacaine, and adrenaline given intrathecally provided excellent analgesia during labour and had a more rapid onset, a longer duration of action, and reduced local anaesthetic requirements compared with epidural administration.[1] Intrathecal sufentanil and bupivacaine provided shorter duration of analgesia when given during the advanced stages of labour compared with early labour.[2] There has been some concern about the effect of intrathecal use on fetal heart rate. An early study[3] found no significant difference in the heart rate when intrathecal sufentanil was compared with epidural bupivacaine; however, a more recent study[4] reported that high-dose intrathecal sufentanil (7.5 micrograms) when given on its own increased the risk of fetal heart rate abnormalities when compared with low-dose intrathecal sufentanil (2.5 micrograms) given with bupivacaine and adrenaline. Nonetheless, there was no evidence of a difference in adverse neonatal outcomes between the groups.

A small study in patients undergoing hip replacement found that intrathecal sufentanil 7.5 micrograms produced better and longer lasting analgesia than the same dose given intravenously.[5]

Intrathecal sufentanil has also been tried in the treatment of chronic pain.[6]

1. Kartawiadi SL, *et al.* Spinal analgesia during labor with low-dose bupivacaine, sufentanil, and epinephrine: a comparison with epidural analgesia. *Reg Anesth* 1996; **21:** 191–6.
2. Viscomi CM, *et al.* Duration of intrathecal labor analgesia: early versus advanced labor. *Anesth Analg* 1997; **84:** 1108–12.
3. Nielsen PE, *et al.* Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. *Anesth Analg* 1996; **83:** 742–6.
4. Van de Velde M, *et al.* Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesth Analg* 2004; **98:** 1153–9.
5. Fournier R, *et al.* Intrathecal sufentanil is more potent than intravenous for postoperative analgesia after total-hip replacement. *Reg Anesth Pain Med* 2005; **30:** 249–54.
6. Waara-Wolleat KL, *et al.* A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med* 2006; **7:** 251–9.

Administration in children. Although experience of paediatric use is limited, sufentanil citrate is licensed for the induction and maintenance of anaesthesia in children under 12 years of age undergoing cardiovascular surgery. Intravenous doses of 10 to 25 micrograms/kg are given with 100% oxygen with maintenance doses of up to 25 to 50 micrograms.

Anaesthesia. Sufentanil, like fentanyl (p.59), appears to produce fewer circulatory changes than morphine, which may offer some advantages in cardiovascular surgery.

Premedication with sufentanil given intranasally has been tried in children[1-3] and in adults.[4]

Sufentanil is one of the opioids that have been used with a neuroleptic to produce *neuroleptanalgesia*.

1. Henderson JM, *et al.* Pre-induction of sufentanil. *Anesthesiology* 1988; **68:** 671–5.
2. Zedie N, *et al.* Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; **59:** 341–8.
3. Bayrak F, *et al.* A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. *J Opioid Manag* 2007; **3:** 74–8.
4. Helmers JHJH, *et al.* Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth* 1989; **36:** 494–7.

Pain. For the epidural or intrathecal use of sufentanil in the management of pain, see above. Intranasal sufentanil has been tried for breakthrough cancer pain[1] and postoperative analgesia.[2] It has also been tried sublingually in the management of breakthrough cancer pain.[3]

1. Jackson K, *et al.* Pilot dose finding study of intranasal sufentanil for breakthrough and incident cancer-associated pain. *J Pain Symptom Manage* 2002; **23:** 450–2.
2. Mathieu N, *et al.* Intranasal sufentanil is effective for postoperative analgesia in adults. *Can J Anesth* 2006; **53:** 60–6.
3. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* 2001; **22:** 627–30.

Sedation. Some references to the use of sufentanil for sedation are given below. See also Anaesthesia, above.

1. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
2. Lefrant JY, *et al.* Sufentanil short duration infusion for postoperative sedation in critically ill patients. *Br J Anaesth* 1995; **74** (suppl 1): 114.
3. Kinirons BP, *et al.* Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerve block. *Anesth Analg* 2000; **90:** 1118–21.

Preparations

USP 31: Sufentanil Citrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Sufenta; ***Austria:*** Sufenta; ***Belg.:*** Sufenta; ***Braz.:*** Fastfen; Sufenta; ***Canad.:*** Sufenta; ***Chile:*** Sufenta; ***Cz.:*** Sufenta; ***Denm.:*** Sufenta; ***Fin.:*** Sufenta; ***Fr.:*** Sufenta; ***Ger.:*** Sufenta; ***Indon.:*** Sufenta; ***Ital.:*** Disufen; Fentatienil; ***Malaysia:*** Sufenta†; ***Neth.:*** Sufenta; ***Norw.:*** Sufenta; ***Port.:*** Sufenta; ***S.Afr.:*** Sufenta; ***Swed.:*** Sufenta; ***Switz.:*** Sufenta; ***Turk.:*** Sufenta; ***USA:*** Sufenta†.

Sulindac *(BAN, USAN, rINN)*

MK-231; Sulindaakki; Sulindaco; Sulindacum; Sulindak; Szulindak.
(*Z*)-[5-Fluoro-2-methyl-1-(4-methylsulphinylbenzylidene)inden-3-yl]acetic acid.

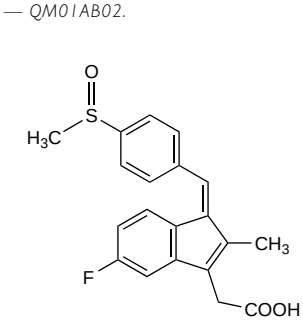
Сулиндак

$C_{20}H_{17}FO_3S$ = 356.4.

CAS — 38194-50-2.

ATC — M01AB02.

ATC Vet — QM01AB02.



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

Ph. Eur. 6.2 (Sulindac). A yellow, polymorphic, crystalline powder. Very slightly soluble in water and in ether; sparingly soluble in alcohol; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Sulindac). A yellow, odourless or practically odourless, crystalline powder. Practically insoluble in water and in hexane; slightly soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; very slightly soluble in ethyl acetate and in isopropyl alcohol.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Urine discoloration has occasionally been reported with sulindac.

Sulindac metabolites have been reported as major or minor components in renal stones. It should therefore be used with caution in patients with a history of renal stones and such patients should be kept well hydrated while receiving sulindac.

UK licensed product information recommends that patients with hepatic impairment should not be given sulindac; in the USA, however, licensed information states that patients with poor hepatic function may be given a reduced dose of sulindac with close monitoring. The dose of sulindac may also need to be reduced in those with renal impairment. Licensed information recommends that sulindac is not used in patients with advanced renal disease, but this appears to be based on a lack of data in such patients.

Effects on the blood. Agranulocytosis,[1] thrombocytopenia,[2] haemolytic anaemia,[3] and aplastic anaemia[4] have been reported in patients taking sulindac.

1. Romeril KR, *et al.* Sulindac induced agranulocytosis and bone marrow culture. *Lancet* 1981; **ii:** 523.
2. Karachalios GN, Parigorakis JG. Thrombocytopenia and sulindac. *Ann Intern Med* 1986; **104:** 128.
3. Johnson FP, *et al.* Immune hemolytic anemia associated with sulindac. *Arch Intern Med* 1985; **145:** 1515–16.
4. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the CNS. Acute deterioration of parkinsonism occurred in a patient after starting sulindac.[1]

See also Hypersensitivity, below.

1. Sandyk R, Gillman MA. Acute exacerbation of Parkinson's disease with sulindac. *Ann Neurol* 1985; **17:** 104–5.

Effects on the endocrine system. A case of reversible gynaecomastia associated with sulindac therapy has been reported.[1] There has also been a report[2] of reversible hypothyroidism in an elderly patient taking sulindac.

1. Kapoor A. Reversible gynecomastia associated with sulindac therapy. *JAMA* 1983; **250:** 2284–5.
2. Iyer RP, Duckett GK. Reversible secondary hypothyroidism induced by sulindac. *BMJ* 1985; **290:** 1788.

Effects on the gallbladder. A "sludge" composed of crystalline metabolites of sulindac has been found in the common bile duct during surgery for biliary obstruction in patients who had been taking sulindac.[1]

1. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the kidneys. Sulindac-induced renal impairment, interstitial nephritis, and nephrotic syndrome have been reported.[1] It has been suggested that sulindac, as a prodrug, may not inhibit renal prostaglandin synthesis in therapeutic doses. However, this potentially important therapeutic advantage has not been uniformly seen in short-term studies in patients with renal dysfunction.[2-4]

There have been reports of renal stones consisting of between 10 and 90% of sulindac metabolites developing in patients given sulindac.[5]

1. Whelton A, *et al.* Sulindac and renal impairment. *JAMA* 1983; **249:** 2892.
2. Klassen DK, *et al.* Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. *J Clin Pharmacol* 1989; **29:** 1037–42.
3. Eriksson L-O, *et al.* Effects of sulindac and naproxen on prostaglandin excretion in patients with impaired renal function and rheumatoid arthritis. *Am J Med* 1990; **89:** 313–21.
4. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. *Ann Intern Med* 1990; **112:** 568–76.
5. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the liver. Hepatotoxicity reported in patients receiving sulindac includes hepatocellular injury and cholestatic jaundice.[1,2] Symptoms of hypersensitivity including rash, fever, or eosinophilia have been reported in 35 to 55% of patients with sulindac-induced liver damage;[2] in these patients the liver damage occurred usually within 4 to 8 weeks of beginning sulindac therapy. For reference to a report citing the strongest evidence for