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.

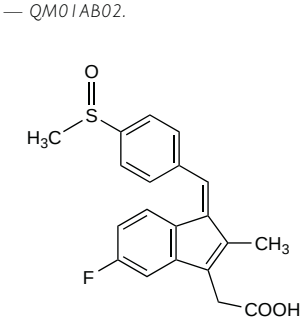
Сулиндак

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

an association of sulindac with liver disease compared with other NSAIDs, see under NSAIDs, p.98.

See also Effects on the Skin, below.

1. Gallanosa AG, Spyker DA. Sulindac hepatotoxicity: a case report and review. *Clin Toxicol* 1985; **23:** 205–38.
2. Tarazi EM, *et al.* Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104:** 569–74.

Effects on the lungs. For reference to pneumonitis associated with sulindac therapy, see Hypersensitivity, below.

Effects on the skin. Toxic epidermal necrolysis has occurred in patients taking sulindac.[1] In a patient toxic hepatitis and the Stevens-Johnson/toxic epidermal necrolysis syndrome resulted in death.[2]

An unusual pernio-like reaction affecting the toes, which was also confirmed by rechallenge, has been reported.[3]

Sulindac has also been reported to cause photosensitivity reactions.[4]

1. Small RE, Garnett WR. Sulindac-induced toxic epidermal necrolysis. *Clin Pharm* 1988; **7:** 766–71.
2. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol* 1983; **10:** 512–13.
3. Reinertsen JL. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24:** 1215.
4. Anonymous. Drugs that cause photosensitivity. *Med Lett Drugs Ther* 1986; **28:** 51–2.

Hypersensitivity. Hypersensitivity reactions to sulindac include pneumonitis,[1,2] generalised lymphadenopathy,[3] aseptic meningitis,[4] and anaphylactoid reaction.[5]

See also Effects on the Liver and Effects on the Skin, above.

1. Smith FE, Lindberg PJ. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244:** 269–70.
2. Fein M. Sulindac and pneumonitis. *Ann Intern Med* 1981; **95:** 245.
3. Sprung DJ. Sulindac causing a hypersensitivity reaction with peripheral and mediastinal lymphadenopathy. *Ann Intern Med* 1982; **97:** 564.
4. Fordham von Reyn C. Recurrent aseptic meningitis due to sulindac. *Ann Intern Med* 1983; **99:** 343–4.
5. Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151:** 387–8.

Pancreatitis. Reports[1-4] of pancreatitis associated with sulindac therapy.

1. Goldstein J, *et al.* Sulindac associated with pancreatitis. *Ann Intern Med* 1980; **93:** 151.
2. Siefkin AD. Sulindac and pancreatitis. *Ann Intern Med* 1980; **93:** 932–3.
3. Lilly EL. Pancreatitis after administration of sulindac. *JAMA* 1981; **246:** 2680.
4. Memon AN. Pancreatitis and sulindac. *Ann Intern Med* 1982; **97:** 139.

Interactions

For interactions associated with NSAIDs, see p.99.

Dimethyl sulfoxide reduces plasma concentrations of the active metabolite of sulindac and use of the two drugs together has also resulted in peripheral neuropathy. Diflunisal and aspirin are reported to reduce the plasma concentration of the active metabolite of sulindac. Unlike other NSAIDs, sulindac is reported not to reduce the antihypertensive effects of drugs such as thiazide diuretics, but nevertheless licensed product information recommends that blood pressure be closely monitored in patients taking antihypertensives with sulindac.

Pharmacokinetics

Sulindac is absorbed from the gastrointestinal tract. It is metabolised by reversible reduction to the sulfide metabolite, which appears to be the active form, and by irreversible oxidation to the sulfone metabolite. Peak plasma concentrations of the sulfide metabolite are achieved in about 2 hours. The mean elimination half-life of sulindac is about 7.8 hours and of the sulfide metabolite about 16.4 hours. Sulindac and its metabolites are over 90% bound to plasma proteins. About 50% is excreted in the urine mainly as the sulfone metabolite and its glucuronide conjugate, with smaller amounts of sulindac and its glucuronide conjugate; about 25% appears in the faeces, primarily as sulfone and sulfide metabolites. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

◊ References.

1. Davies NM, Watson MS. Clinical pharmacokinetics of sulindac: a dynamic old drug. *Clin Pharmacokinet* 1997; **32:** 437–59.

Uses and Administration

Sulindac is an NSAID (p.99) structurally related to indometacin (p.68); its activity appears to be due to its sulfide metabolite. Sulindac is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and also in the short-term management of acute gout and peri-articular conditions such as bursitis and tendinitis. It has also been used to reduce fever.

A usual initial oral dose of sulindac is 150 or 200 mg twice daily, reduced according to response; the maximum recommended daily dose is 400 mg. Licensed product information recommends that the treatment of peri-articular disorders should be limited to 7 to 14 days; for acute gout, 7 days of therapy is usually adequate.

Sulindac sodium has been given by rectal suppository.

Administration in hepatic or renal impairment. The dose of sulindac may need to be reduced in patients with hepatic or renal impairment but see Adverse Effects and Precautions, above..

Gastrointestinal disorders. In placebo-controlled studies[1,2] sulindac 150 to 200 mg twice daily for 6 to 9 months has reduced the number and size of polyps in patients with familial adenomatous polyposis but the effect may be incomplete and in a study[2] only polyps less than 2 mm in size regressed. In addition, the size and number of polyps has been reported[1] to increase on stopping treatment. The benefit of long-term therapy has therefore been studied. Reduced effectiveness has been seen[3] with long-term use but others[4] have reported management of recurrences by adjustment of maintenance dosage; there seemed to be individual variations in sensitivity to sulindac with respect to prevention of polyp recurrence although an average maintenance dose of 200 mg daily appeared to be needed.[4]

There is evidence[5] that sulindac alters the ratio of apoptosis of surface cells relative to those lying deeper in the crypt of rectal mucosa, thus altering epithelial homoeostasis. Whether sulindac prevents malignant degeneration is unknown but there have been reports[6-8] of patients who developed rectal cancer during or after long-term therapy for adenomatous polyposis. A more recent, placebo-controlled trial[9] has also reported that sulindac did not reduce the development of adenomas in patients with familial adenomatous polyposis. Some[1,9] consider that sulindac is unlikely to replace surgery as primary therapy for familial adenomatous polyposis.

A sulfone metabolite of sulindac, exisulind (p.720) has also been investigated for the treatment of familial adenomatous polyposis.

Sulindac has also been reported to have produced beneficial effects in a patient with duodenal polyps associated with Gardner's syndrome[10] but a placebo-controlled study has suggested that it may not be effective against sporadic type colonic polyps.[11]

For a discussion of evidence suggesting that regular use of NSAIDs may protect against various types of malignant neoplasms of the gastrointestinal tract, see Malignant Neoplasms in NSAIDs, p.100.

1. Giardiello FM, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328:** 1313–16.
2. Debinski HS, *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; **345:** 855–6.
3. Tonelli F, Valanzano R. Sulindac in familial adenomatous polyposis. *Lancet* 1993; **342:** 1120.
4. Labayle D, *et al.* Sulindac in familial adenomatous polyposis. *Lancet* 1994; **343:** 417–18.
5. Keller JJ, *et al.* Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac. *Gut* 1999; **45:** 822–8.
6. Thorson AG, *et al.* Rectal cancer in FAP patient after sulindac. *Lancet* 1994; **343:** 180.
7. Matsuhashi N, *et al.* Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. *Am J Gastroenterol* 1998; **93:** 2261–6.
8. Cruz-Correa M, *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002; **122:** 641–5.
9. Giardiello FM, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002; **346:** 1054–9.
10. Parker AL, *et al.* Disappearance of duodenal polyps in Gardner's syndrome with sulindac therapy. *Am J Gastroenterol* 1993; **88:** 93–4.
11. Ladenheim J, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995; **108:** 1083–7.

Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective $beta_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Sulindac has also been tried[1,2] as an alternative to indometacin as it appears to have little placental transfer and may therefore have fewer fetal adverse effects.[1] However, the authors of a subsequent study suggested that sulindac had many of the same adverse fetal effects as indometacin and its use could only be described as investigational.[3] A study[4] using relatively low doses of sulindac (100 mg twice daily) did not note any significant fetal or maternal adverse effects but also found the drug to be ineffective in extending gestation or improving outcome.

1. Carlan SJ, *et al.* Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. *Obstet Gynecol* 1992; **79:** 223–8.
2. Carlan SJ, *et al.* Outpatient oral sulindac to prevent recurrence of preterm labor. *Obstet Gynecol* 1995; **85:** 769–74.
3. Kramer WB, *et al.* A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999; **180:** 396–401.
4. Humphrey RG, *et al.* Sulindac to prevent recurrent preterm labor: a randomized controlled trial. *Obstet Gynecol* 2001; **98:** 555–62.

Preparations

BP 2008: Sulindac Tablets;
USP 31: Sulindac Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Aclin; Clinoril†; ***Austria:*** Clinoril; ***Belg.:*** Clinoril; ***Canad.:*** Apo-Sulin; Novo-Sundac; ***Cz.:*** Clinoril†; ***Denm.:*** Clinoril†; ***Fr.:*** Arthrocine; ***Hong Kong:*** Aclin; Clinoril; ***Irl.:*** Clinoril; ***Ital.:*** Algocetil; Clinoril; Sulen†; ***Malaysia:*** Aclin†; Apo-Sulin†; Clinoril†; ***Mex.:*** Atriser; Bio-Dac; Clinoril; Clison; Copal; Kenalin; Renidac; Sulifur; Vindacin; ***Norw.:*** Clinoril; ***NZ:*** Clinoril; Daclin; ***Port.:*** Artribid; ***Singapore:*** Apo-Sulin; ***Spain:*** Sulindal; ***Swed.:*** Clinoril; ***Switz.:*** Clinoril†; ***Thai.:*** Cenlidac; Clinoril; ***UK:*** Clinoril; ***USA:*** Clinoril; ***Venez.:*** Clinoril†.

Superoxide Dismutase

SOD; Superóxido dismutasa.

Description. Superoxide dismutase represents a group of water-soluble protein congeners widely distributed in nature which catalyse the conversion of superoxide radicals to peroxide. Several different forms exist, which vary in their metal content; forms containing copper or copper and zinc are common.

Orgotein *(BAN, USAN, rINN)*

Bovine Superoxide Dismutase; Orgoteiini; Orgoteína; Orgotéine; Orgoteinum; Ormetein.

Орготеин

CAS — 9016-01-7.
ATC — M01AX14.
ATC Vet — QM01AX14.

Description. Orgotein is a superoxide dismutase produced from beef liver as Cu-Zn mixed chelate. Mol. wt about 33 000 with a compact conformation maintained by about 4 gram-atoms of chelated divalent metal.

Pegorgotein *(USAN, rINN)*

Pegorgoteína; Pégorgotéine; Pegorgoteinum; PEG-SOD; Win-22118.

Пэгоротеин

CAS — 155773-57-2.

Description. Pegorgotein is a superoxide dismutase conjugated with polyethylene glycol to prolong its duration of action.

Sudismase *(rINN)*

Sudismasa; Sudismasum.

Судизмаза

CAS — 110294-55-8.

Description. Sudismase is a human *N*-acetylsuperoxide dismutase produced by recombinant DNA technology and containing a copper and zinc prosthetic group.

Adverse Effects

Anaphylaxis and other hypersensitivity reactions, sometimes fatal, have been reported with orgotein. Local reactions and pain may occur at the site of injection of orgotein.

Pharmacokinetics

◊ References.

1. Tsao C, *et al.* Pharmacokinetics of recombinant human superoxide dismutase in healthy volunteers. *Clin Pharmacol Ther* 1991; **50:** 713–20.
2. Uematsu T, *et al.* Pharmacokinetics and safety of intravenous recombinant human superoxide dismutase (NK341) in healthy subjects. *Int J Clin Pharmacol Ther* 1994; **32:** 638–41.
3. Jadot G, *et al.* Clinical pharmacokinetics and delivery of bovine superoxide dismutase. *Clin Pharmacokinet* 1995; **28:** 17–25.
4. Rosenfeld WN, *et al.* Safety and pharmacokinetics of recombinant human superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1996; **97:** 811–17.
5. Davis JM, *et al.* Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1997; **100:** 24–30.
6. Schwedhelm E, *et al.* Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. *Clin Pharmacokinet* 2003; **42:** 437–59.

Uses and Administration

Superoxide dismutases have anti-inflammatory properties. Orgotein, a bovine derived superoxide dismutase, has been given by local injection, into the joints for degenerative joint disorders, but hypersensitivity reactions have limited its use. It has also been tried for the amelioration of adverse effects from radiotherapy. Forms of human superoxide dismutase derived by recombinant DNA technology have been developed.