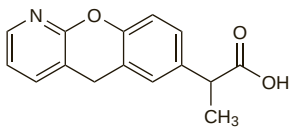
Pranoprofen *(rINN)*

Pranoprofène; Pranoprofeno; Pranoprofenum. α-Methyl-5*H*-[1]benzopyrano[2,3-*b*]pyridine-7-acetic acid.

Пранопрофен

$C_{15}H_{13}NO_3$ = 255.3.
CAS — 52549-17-4.
ATC — S01BC09.
ATC Vet — QS01BC09.



Pharmacopoeias. In *Jpn.*

Profile
Pranoprofen, a propionic acid derivative, is an NSAID (p.96). It is used as eye drops in a concentration of 0.1% for ocular inflammation. Pranoprofen has also been given orally for the treatment of pain, inflammation, and fever.

◊ References.

1. Notivol R, *et al.* Treatment of chronic nonbacterial conjunctivitis with a cyclo-oxygenase inhibitor or a corticosteroid. *Am J Ophthalmol* 1994; **117**: 651–6.

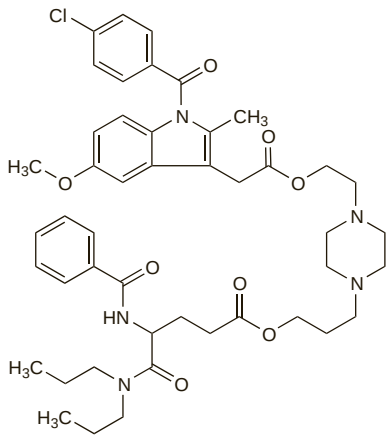
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Pranox; ***Braz.:*** Difen; ***Gr.:*** Pranofen; ***Ital.:*** Oftalar; Pranoflog; ***Jpn:*** Niflan; ***Port.:*** Oftalar; ***Spain:*** Oftalar; ***Turk.:*** Oftalar.

Proglumetacin Maleate *(BANM, rINNM)*

CR-604; Maleato de proglumetacina; Proglumétacine, Maléate de; Proglumetacinum Maleas; Protacine Maleate. 3-{4-[2-(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-ylacetoxy)ethyl]piperazin-1-yl}propyl 4-benzamido-*N*,*N*-dipropylglutaramate dimaleate.

Проглуметацина Малеат

$C_{46}H_{58}ClN_5O_8,2C_4H_4O_4$ = 1076.6.
CAS — 57132-53-3 (proglumetacin); 59209-40-4 (proglumetacin maleate).
ATC — M01AB14.
ATC Vet — QM01AB14.



(proglumetacin)

Profile
Proglumetacin maleate, an indoleacetic acid derivative related to indometacin (p.66), is an NSAID (p.96). It has been used in musculoskeletal and joint disorders in oral doses of up to 600 mg daily, in divided doses. Proglumetacin maleate has also been given as rectal suppositories and topically as a 5% cream.

◊ References.

1. Appelboom T, Franchimont P. Proglumetacin versus indometacin in rheumatoid arthritis: a double-blind multicenter study. *Adv Therapy* 1994; **11:** 228–34.
2. Martens M. Double-blind randomized comparison of proglumetacin and naproxen sodium in the treatment of patients with ankle sprains. *Curr Ther Res* 1995; **56:** 639–48.

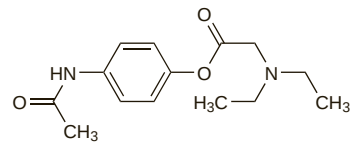
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Alaidol†; Bruxel; ***Belg.:*** Tolindol; ***Chile:*** Afloxan†; ***Ger.:*** Protaxon; ***Hong Kong:*** Afloxan; ***Ital.:*** Afloxan; Proxil; ***Jpn:*** Miridacin; ***Philipp.:*** Afloxan; ***Port.:*** Protaxil; ***Spain:*** Prodamox; ***Thai.:*** Afloxan.

Propacetamol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propacetamol; Propacétamol, chlorhydrate de; Propacetamol-hidroklorid; Propacetamol-hydrochlorid; Propacetamolhydroklorid; Propacetamoli hydrochloridum; Propacetamolio hidrochloridas; Propasetamolihydrokloridi. The hydrochloride of *N*,*N*-diethylglycine ester with paracetamol; 4-Acetamidophenyl diethylaminoacetate hydrochloride.

Пропацетамола Гидрохлорид

$C_{14}H_{20}N_2O_3$,HCl = 300.8.
CAS — 66532-85-2 (propacetamol).
ATC — N02BE05.
ATC Vet — QN02BE05.



(propacetamol)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Propacetamol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. Protect from moisture.

Profile
Propacetamol hydrochloride, a para-aminophenol derivative, is hydrolysed to paracetamol (p.108) in the plasma. It has been given intramuscularly or intravenously in usual doses of 1 to 2 g every 4 hours up to 4 times daily if necessary, to a maximum dose of 8 g daily, for the treatment of pain (see Choice of Analgesic, p.2) and fever (p.10). For doses in children, see below.

Administration in children. In some countries propacetamol is used intravenously in the treatment of pain and fever in neonates and children.[1,2] Doses range from 20 to 30 mg/kg given over 15 minutes up to 4 times daily, not exceeding a maximum daily dose of 120 mg/kg propacetamol (equivalent to a daily dose of 60 mg/kg of paracetamol).

1. Allegaert K, *et al.* Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F25–F28.
2. Walson PD, *et al.* Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28:** 762–9.

Adverse effects. Occupational contact dermatitis has been reported in healthcare professionals after preparing injections of propacetamol.[1-3]

Propacetamol is the hydrochloride of *N*,*N*-diethylglycine ester with paracetamol and the results of a study[4] have suggested that allergic reactions to propacetamol are related to sensitisation to the activated ester rather than to paracetamol itself.

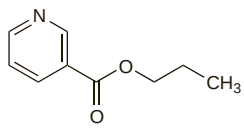
1. Barbaud A, *et al.* Occupational allergy to propacetamol. *Lancet* 1995; **346:** 902.
2. Szczurko C, *et al.* Occupational contact dermatitis from propacetamol. *Contact Dermatitis* 1996; **35:** 299–301.
3. Gielen K, *et al.* Occupational allergic contact dermatitis from drugs in healthcare workers *Contact Dermatitis* 2001; **45:** 273–9.
4. Berl V, *et al.* Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated *N*,*N*-diethylglycine. *Contact Dermatitis* 1998; **38:** 185–8.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Pro-Dafalgan†; ***Denm.:*** Pro-Dafalgan†; ***Fin.:*** Pro-Dafalgan†; ***Gr.:*** Pro-Dafalgan; Pro-depon†; ***Israel:*** Pro-Dafalgan†; ***Ital.:*** Pro-Efferalgan†; ***Mex.:*** Tempra†; ***Norw.:*** Pro-Dafalgan; ***Port.:*** Pro-Dafalgan†; ***Spain:*** Pro-Efferalgan†; ***Swed.:*** Pro-Dafalgan†; ***Switz.:*** Pro-Dafalgan†.

Propyl Nicotinate

Nicotinato de propilo.

$C_9H_{11}NO_2$ = 165.2.
CAS — 7681-15-4.



Profile
Propyl nicotinate is used in topical preparations as a rubefacient.

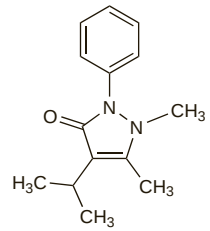
Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Elacur; Nicodan†.

Propyphenazone *(BAN, rINN)*

Isopropylantipyrine; Isopropylantipyrinum; Isopropylphenazone; Propifenazon; Propifenazona; Propifenazonas; Propyfenatsoni; Propyfenazon; Propyphénazone; Propyphenazonum. 4-Isopropyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

Пропифеназон

$C_{14}H_{18}N_2O$ = 230.3.
CAS — 479-92-5.
ATC — N02BB04.
ATC Vet — QN02BB04.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Propyphenazone). A white or slightly yellowish crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile
Propyphenazone, a pyrazolone derivative related to phenazone (p.116), has analgesic and antipyretic properties. It has been given orally and as a rectal suppository in the treatment of pain and fever. The usual oral adult dose is 0.5 to 1 g up to four times daily. There have been some reports of severe hypersensitivity reactions in patients receiving propyphenazone.

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

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Dim-Antos; ***Ger.:*** Demex; Eufibron†; Hewedolor propy†; Isoprochin P†.

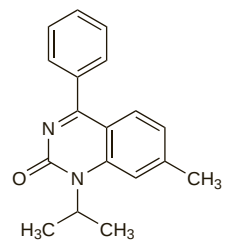
Multi-ingredient: ***Arg.:*** Algio-Bladuril; Espasmo Cibalena; Saridon; ***Austria:*** Adolorin; APA; Avamigran; Coldagrippin; Contraforte†; Eu-Med; Gewadal; Melabon; Migradon; Montamed; Nervan; Rapidol; Saridon; Spasmoplus; Tonopan; Toximer; Vivimed; Waldheim Influvidon; Waldheim Schmerztabletten; ***Belg.:*** Kranit Nova†; Optalidon†; Saridon†; Spasmoplus†; ***Braz.:*** Saridon; Tonopan; ***Chile:*** Abalgin; Droxel; Espasmo Cibalgina; Espasmo Cibalgina Compuesta; Feminosan†; Gripasan Compuesto; Immediat†; SAE; ***Cz.:*** Saridon; Spasmoveralgin Neo†; Valetol; ***Denm.:*** Kodamid; ***Ger.:*** Avamigran N†; Cibalgin Compositum N†; Copyrkal N†; Ergo-Kranit†; Eudorlin†; Fomagrippin N†; Ichtho-Bellol compositum S†; Migrane-Kranit Duo†; Migrane-Kranit N†; Migratan S†; Norgesic N†; Optalidon N; Optalidon special NOC†; RubieNex spezial†; Saridon; Schworalgan; Spasmo-Cibalgin S†; Titretta S; ***Hong Kong:*** Epizon†; Saridon; Tonterin†; ***Hung.:*** Saridon; Trinell Pro; ***Indon.:*** Butamidon; Cetapyrin; Enkapyrin; Migran; Paramex; Saridon; ***Ital.:*** Cistalgan; Influrem†; Influvit; Micranet†; Mindol-Merck†; Neo-Optalidon; Odontalgico Dr. Knapp con Vit. B1; Optalidon; Saridon; Sedol; Spasmo-Cibalgina†; Spasmoplus; Uniplus; Veramon; ***Mex.:*** Espasmo Cibalgina; Tonopan; ***Neth.:*** Daro Hoofdpijnpoeders; Kruidvat; Para-don; Sanalgin; Saridon; ***Pol.:*** Analget; Cefalgin; Gardan P; Krople Zoladkowe; Pabialgin P; Saridon; ***Port.:*** Avamigran†; Optalidon; Saridon N; ***Rus.:*** Caffetin (Каффетин); Coffedon (Коффедон); Gewadal (Гевадал); Kofan (Кофан); Saridon (Саридон); ***S.Afr.:*** Ilvico; ***Spain:*** Abdominol; Calmoplex; Dolodens; Flexagil†; Hubergrip†; Melabon; Meloka; Optalidon; Quimpedor; Saridon; Sedalmerck†; Sulmetin Papaver; Sulmetin Papaverina†; Tabletas Quimpe; Tonopan; ***Switz.:*** Barbamin†; Caposan†; Cerebrol†; Comprimes analgesiques "S"†; Dialgine forte†; Dolopyrine†; Dolostop†; Escalgin sans codeine†; Escogripp sans codeine; Gewodine†; Nicaphlogy†; Saridon†; Seranex sans codeine†; Sinedal†; Spasmo-Barbamin†; Spasmo-Barbamine compositum†; Spasmo-Cibalgin comp†; Spasmo-Cibalgin†; Spedralgin sans codeine†; Tonopan†; ***Turk.:*** Aljil; Bioptan; Minoset Plus; Panalgine.

Proquazone *(BAN, USAN, rINN)*

43-715; Procuazona; Prokuazon; Prokvatsoni; Prokvazon; Proquazonum; RU-43-715-n. 1-Isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one.

Проквазон

$C_{18}H_{18}N_2O$ = 278.3.
CAS — 22760-18-5.
ATC — M01AX13.
ATC Vet — QM01AX13.



Profile
Proquazone is an NSAID (p.96) that has been used orally and rectally in musculoskeletal and joint disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Hung.: Biarison†; ***Turk.:*** Biarison.

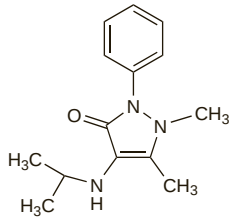
Ramifenazone *(rINN)*

Isopropylaminophenazone; Isopyrin; Ramifenazona; Ramifénazone; Ramifenazonum. 4-Isopropylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

Рамифеназон

$C_{14}H_{19}N_3O$ = 245.3.

CAS — 3615-24-5.



NOTE. The name Isopyrin has also been applied to isoniazid.

Profile
Ramifenazone is an NSAID (p.96) that has been used in preparations for painful and inflammatory conditions; it has also been used in veterinary medicine. Ramifenazone has been given as the hydrochloride and the salicylate.

Remifentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

GI-87084B; Hidrocloruro de remifentanilo; Rémifentanil, Chlorhydrate de; Remifentanili Hydrochloridum. 4-Carboxyl-4-(*N*-phenylpropionamido)-1-piperidine propionic acid dimethyl ester monohydrate.

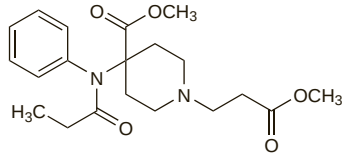
Ремифентанила Гидрохлорид

$C_{20}H_{28}N_2O_5$,HCl = 412.9.

CAS — 132539-07-2.

ATC — N01AH06.

ATC Vet — QN01AH06.



(remifentanil)

Incompatibility. Remifentanil hydrochloride should not be mixed in the same intravenous solution as blood products. UK licensed product information states that it should not be mixed with lactated Ringer's injection with or without 5% glucose; however, in the USA the product literature states that remifentanil hydrochloride is stable for 4 hours at room temperature after reconstitution and dilution to 20 to 250 micrograms/mL with lactated Ringer's injection and for 24 hours if lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanil 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 0.6 mg/mL and remifentanil 250 micrograms/mL (as the hydrochloride) in 5% glucose.[1]

1. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Dependence and Withdrawal
As for Opioid Analgesics, p.101.

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

Precautions
As for Opioid Analgesics in general, p.103.

Administration. Remifentanil hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

Hepatic impairment. Although the pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment, such patients may be more sensitive to the respiratory depressant effects and should be monitored with doses titrated to individual requirements.

Renal impairment. The pharmacokinetics of remifentanil are not changed in patients with severe renal impairment (a creatinine clearance of less than 10 mL/minute) and licensed product information states that the carboxylic acid metabolite is unlikely to accumulate to clinically active concentrations in such patients after remifentanil infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies[1,2] in intensive care patients with renal impairment given remifentanil infusions at a rate of 100 to 150 nanograms/kg per minute for up to 3 days.

1. Breen D, *et al.* Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; **8:** R21–R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *Br J Anaesth* 2004; **92:** 493–503.

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

Pharmacokinetics
After parenteral doses remifentanil hydrochloride has a rapid onset and short duration of action. Its effective biological half-life is about 3 to 10 minutes and is independent of dose. Remifentanil is about 70% bound to plasma proteins, mainly to α_1-acid glycoprotein. It is hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite. About 95% of a dose of remifentanil is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanil may cross the placenta and is distributed into breast milk.

◊ Licensed product information for remifentanil gives values for a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes.

References.

1. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; **29:** 80–94.
2. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. *Curr Opin Anaesthesiol* 2000; **13:** 449–55.
3. Ross AK, *et al.* Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; **93:** 1393–1401.

Uses and Administration
Remifentanil, an anilidopiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is a short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anaesthesia. It is also used to provide analgesia into the immediate postoperative period, and may be used as the analgesic component of local or regional anaesthesia with or without benzodiazepine sedation. Remifentanil is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care.

Remifentanil is given intravenously as the hydrochloride, usually by infusion. Its onset of action is within 1 minute and the duration of action is 5 to 10 minutes. Doses are expressed in terms of the base; remifentanil hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanil. Initial doses for anaesthesia in elderly patients should be half the recommended adult doses and then titrated to individual requirements. Obese patients may require doses based on their ideal (lean) bodyweight. For details of doses in children, see below.

When used to provide **analgesia** during *induction* of anaesthesia an intravenous infusion is given in doses of 0.5 to 1 micrograms/kg per minute. An additional initial intravenous bolus of 1 microgram/kg may be given over 30 to 60 seconds particularly if the patient is to be intubated less than 8 minutes after the start of the infusion.

For provision of analgesia during *maintenance* of anaesthesia in ventilated patients, usual infusion doses range from 0.05 to 2 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response. Supplemental intravenous boluses of 0.5 to 1 micrograms/kg may be given every 2 to 5 minutes in response to light anaesthesia or intense surgical stress. The infusion dosage in spontaneous respiration is initially 0.04 micrograms/kg per minute adjusted according to response within a usual range of 0.025 to 0.1 micrograms/kg per minute. Bolus doses are not recommended during spontaneous ventilation.

For continuation of analgesia into the immediate *postoperative* period typical doses by intravenous infusion have ranged from 100 to 200 nanograms/kg per minute; supplemental intravenous bolus doses are not recommended during the postoperative period.

To provide **analgesia and sedation** in ventilated patients under intensive care, remifentanil is given as an intravenous infusion at an initial rate of 100 to 150 nanograms/kg per minute. Doses should then be titrated to provide adequate analgesia and sedation; a period of 5 minutes should be allowed between dose adjustments. Additional sedative drugs should be given to those patients inadequately sedated with remifentanil infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanil infusion may be necessary if additional analgesia is required to cover stimulating or painful procedures such as wound dressing. Doses of up to 750 nanograms/kg per minute have been given to some patients. Bolus doses of remifentanil are not recommended in intensive care.

Remifentanil is also used as an analgesic in patients receiving monitored anaesthesia care. In the USA, it may be given intravenously in a single dose of 1 microgram/kg 90 seconds before the local anaesthetic; alternatively, a dose of 100 nanograms/kg per minute may be given as an intravenous infusion, starting 5 minutes before the local anaesthetic, which should be reduced to 50 nanograms/kg per minute after the local anaesthetic. Subsequent adjustments of 25 nanograms/kg per minute at 5-minute intervals may be made to maintain a balanced analgesia.

Remifentanil has a very rapid offset of action and no residual opioid action remains 5 to 10 minutes after stopping an infusion. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

◊ References and reviews.

1. Patel SS, Spencer CM. Remifentanil. *Drugs* 1996; **52:** 417–27.
2. Duthie DJR. Remifentanil and tramadol. *Br J Anaesth* 1998; **81:** 51–7.
3. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. *Clin Pharmacokinet* 2005; **44:** 787–96.
4. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; **65:** 1793–1823. Correction. *ibid.*; 2286.
5. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006; **66:** 365–85.
6. Welzing L, Roth B. Experience with remifentanil in neonates and infants. *Drugs* 2006; **66:** 1339–50.

Administration in children. Remifentanil hydrochloride, given by continuous intravenous infusion, is used for analgesia during maintenance of general anaesthesia in children. Usual infusion doses (expressed as the base) for those aged from 1 to 12 years range from 0.05 to 1.3 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response; supplemental intravenous boluses of 1 microgram/kg may be given over at least 30 seconds. US licensed product information also states that neonates and children aged up to 2 months may be given infusion doses of 0.4 to 1 micrograms/kg per minute with supplemental boluses of 1 microgram/kg. Similar doses are suggested in the *BNFC* for use in neonates although in the UK remifentanil is not licensed for use in children under 1 year of age.