

**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:** Biaronit; **Turk:** Biaron.

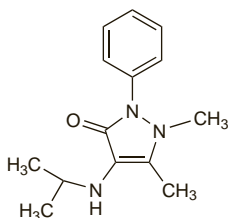
**Ramifenazone** (HINN)

Isopropylaminophenazone; Isopyrin; Ramifenazona; Ramifénazona; 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.

**Remifentanyl Hydrochloride**

(BANM, USAN, rINNM) ⓧ

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

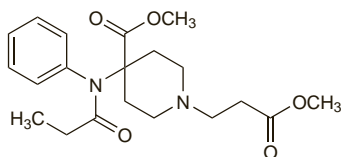
Ремифентанил Гидрохлорид

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

CAS — 132539-07-2.

ATC — N01AH06.

ATC Vet — QN01AH06.



(remifentanyl)

**Incompatibility.** Remifentanyl 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 remifentanyl 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 for lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanyl 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 0.6 mg/mL and remifentanyl 250 micrograms/mL (as the hydrochloride) in 5% glucose.<sup>1</sup>

1. Trissel LA, *et al.* Compatibility of remifentanyl 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.** Remifentanyl hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

**Hepatic impairment.** Although the pharmacokinetics of remifentanyl 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 remifentanyl 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 remifentanyl infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies<sup>1,2</sup> in intensive care patients with renal impairment given remifentanyl 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 remifentanyl in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; **8**: R21-R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanyl and its major metabolite, remifentanyl 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 remifentanyl 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. Remifentanyl is about 70% bound to plasma proteins, mainly to  $\alpha_1$ -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 remifentanyl is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanyl may cross the placenta and is distributed into breast milk.

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

**Uses and Administration**

Remifentanyl, an anilidopiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is a short-acting  $\mu$ -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. Remifentanyl is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care.

Remifentanyl 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; remifentanyl hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanyl. 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) body-weight. 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 post-operative 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, remifentanyl 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 remifentanyl infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanyl 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 remifentanyl are not recommended in intensive care.

Remifentanyl 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.

Remifentanyl 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 remifentanyl, in sufficient time to provide continuous and more prolonged pain relief.

**◇ References and reviews.**

1. Patel SS, Spencer CM. Remifentanyl. *Drugs* 1996; **52**: 417-27.
2. Duthie DJR. Remifentanyl 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 remifentanyl. *Clin Pharmacokinet* 2005; **44**: 787-96.
4. Scott LJ, Perry CM. Remifentanyl: 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. Remifentanyl: 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 remifentanyl in neonates and infants. *Drugs* 2006; **66**: 1339-50.

**Administration in children.** Remifentanyl 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 remifentanyl is not licensed for use in children under 1 year of age.