

**Package leaflet: Information for the user Remifentanil 1 mg powder for concentrate for solution for injection/infusion**

**Remifentanil 2 mg powder for concentrate for solution for injection/infusion**

**Remifentanil 5 mg powder for concentrate for solution for injection/infusion**

remifentanil

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their sign of illness are the same as yours.
- If you get any of the side effects talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet, see section 4.

**What is in this leaflet:**

1. What Remifentanil is and what it is used for
2. What you need to know before you use Remifentanil
3. How to use Remifentanil
4. Possible side effects
5. How to store Remifentanil
6. Contents of the pack and other information

**1. What Remifentanil is and what it is used for**

Remifentanil belongs to a group called opioids. It differs from other medicines in this group by its very quick onset and very short duration of action.

- Remifentanil may be used to stop you feeling pain before or while you are having an operation.
- Remifentanil may be used to relieve pain while you are under controlled mechanical ventilation in an Intensive Care Unit (for patients 18 years of age and over).

**2. What you need to know before you use Remifentanil**

**Do not use Remifentanil**

- if you are allergic (hypersensitive) to remifentanil, any of the other ingredients of this medicine (see list of ingredients in Section 6) or fentanyl derivatives (such as alfentanil, fentanyl, sufentanil). An allergic reaction may include rash, itching, difficulty of breathing or swelling of the face, lips, throat or tongue. You may know this from earlier experience
- as injection into the spinal canal
- as sole medicine to initiate anaesthesia

**Warning and precautions**

Talk to your doctor, pharmacist or nurse before you using Remifentanil if you:

- ever had any adverse reactions during an operation
- ever had any allergic reactions or if you have been told that you are allergic to:
  - o any medicines used during an operation
  - o opioid medicines (e.g., morphine, fentanyl, pethidine, codeine) , see also section above **“Do not use Remifentanil”**
- suffer from impaired lung and/or liver function (you may be more sensitive for breathing difficulties)

Elderly or weak patients (caused by decreased blood volume and/or low blood pressure) are more sensitive to suffer from cardiac or circulatory disturbances.

- As with other opioids remifentanil may produce dependency.

- Following anesthesia with Remifentanyl, you should leave home only accompanied and you should not drink alcohol.
- Remifentanyl should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, and by persons specifically trained in the use of anaesthetic medicines and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation.
- In ventilated intensive care patients the use of Remifentanyl for more than 3 days is not recommended.
- Due to the rapid offset of action of remifentanyl, patients may emerge rapidly from anaesthesia and no residual opioid activity will be present within 5-10 minutes after the discontinuation of Remifentanyl. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Remifentanyl
- At the doses recommended muscle rigidity may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, bolus injections should be administered over not less than 30 seconds.

Hypotension and bradycardia may be managed by reducing the rate of infusion of Remifentanyl or the dose of concurrent anaesthetics or by using intravenous fluids, vasopressor or anticholinergic agents.

### **Drug abuse**

As with other opioids remifentanyl may produce dependency.

### **Children**

Remifentanyl is not recommended in neonates and infants (children under the age of one year). There is little experience of use of Remifentanyl to treat children in intensive care units.

### **Elderly**

If used for an operation under general anaesthesia, the initial dose of Remifentanyl should be appropriately reduced in elderly patients.

### **Other medicines and Remifentanyl**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

This is especially important with the following medicines as they may interact with your Remifentanyl:

- medicines for blood pressure or heart problems (known as beta-blockers or calcium channel blockers). These medicines may increase the effect of Remifentanyl on your heart (lowering of your blood pressure and your heart beat).
- other sedative medicines, such as benzodiazepines. Your doctor or pharmacist will alter the dose of these medicines when you are being given Remifentanyl.

It may still be all right for you to receive Remifentanyl and your doctor will be able to decide what is suitable for you.

Remifentanyl is not metabolized by plasmacholinesterase, therefore, interactions with medicines metabolized by this enzyme are not anticipated.

### **Remifentanyl with food, drink and alcohol**

After having received Remifentanyl you should not drink alcohol until fully recovered.

### **Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given to you.

Your doctor will discuss the possible risks and benefits of being given Remifentanyl if you are pregnant or breast-feeding.

Remifentanyl should not be given to pregnant women unless medically justified. Remifentanyl is not recommended during labour or a Caesarian section.

It is recommended that you stop breast-feeding for 24 hours after Remifentanyl has been given to you.

### **Driving and using machines**

This medicine is only used in hospitalized patients. If you are discharged early, after you have been given Remifentanyl, you must not drive, operate machinery, or work in dangerous situations. You should not go home alone. Your doctor will advise you when it is safe to resume these activities.

This medicine can affect your ability to drive. Do not drive whilst taking this medicine until you know how this medicine affects you. It may be an offence to drive if your ability to drive safely is affected. There is further information for patients who are intending to drive in Great Britain – go to <https://www.gov.uk/drug-driving-law>

### **Remifentanyl contains:**

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

## **3. How to take Remifentanyl**

### **How your injection is given**

You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so.

Method of administration:

Remifentanyl can be given:

- as a single injection into your vein
- as a continuous infusion into your vein. This is where the drug is slowly given to you over a longer period of time.

Dose

The way you are given the drug and the dose you receive will depend on:

- your weight
- the operation you have
- how much pain you will be in
- how sleepy the medical staff want you to be in the Intensive Care Unit. The dose varies from one patient to another.

### **If you are given too much or too little of Remifentanyl**

The effects of Remifentanyl are carefully monitored throughout your operation and in intensive care, and appropriate action will be taken promptly if you receive too much or too little.

### **After your operation**

Tell your doctor or nurse if you are in pain. If you are in pain after your procedure, they will be able to give you other painkillers.

If you have any further questions or concerns on the use of this medicine, ask your doctor or nurse.

## **4. Possible side effects**

Like all medicines, Remifentanyl can cause side effects, although not everybody gets them.

The following side effects have been reported:

Very common (may affect more than 1 in 10 people)

- muscle stiffness
- feeling sick (nausea)
- being sick (vomiting)
- low blood pressure (hypotension)

Common (may affect up to 1 to 10 people)

- slow heart beat (bradycardia)
- shallow breathing (respiratory depression)
- breathing stops (apnoea)
- itching
- shivering after the operation
- high blood pressure (hypertension) after the operation

Uncommon (may affect up to 1 in 100 people)

- constipation
- pain after the operation
- oxygen deficiency (hypoxia)

Rare (may affect up to 1 to 1000 people)

- slow heart beat followed by heart block in patients receiving remifentanyl with one or more anaesthetic medicines
- sleepiness (during recovering from the operation)
- severe allergic reactions including shock, circulatory failure and heart attack in patients receiving remifentanyl with one or more anaesthetic medicines

Not known (frequency cannot be estimated from the available data)

- fits
- abnormal heart rhythm due to heart block
- remifentanyl having less effect than normal (drug tolerance)

As with other medicines of this class (opioids), long-term use of Remifentanyl can lead to dependence. Please ask your doctor for advice.

### **Reporting of side effects**

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Remifentanyl**

Keep this medicine out of the sight and reach of children.

Do not use Remifentanyl after the expiry date which is stated on the carton / vial after "EXP". The expiry date refers to the last day of that month.

### **Unopened medicinal product**

1 mg: Do not store above 25° C.

2 mg: Do not store above 25° C.

5 mg: Do not store above 25° C.

Do not refrigerate or freeze.

1 mg: Keep the vial in the outer carton in order to protect from light.

## Reconstituted / diluted medicinal product

After reconstitution:

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After dilution:

Following dilution, the solution must be inspected visually to ensure that it is clear, colourless and virtually free from solids, and that there is no damage to the vials. If such changes are detected, the solution must be discarded.

The diluted product should be used immediately.

The diluted solution is for single use only.

Any unused solution must be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What Remifentanil contains

The active substance is:

remifentanil (as hydrochloride)

1 vial contains 1 mg remifentanil (as remifentanil hydrochloride).

1 vial contains 2 mg remifentanil (as remifentanil hydrochloride).

1 vial contains 5 mg remifentanil (as remifentanil hydrochloride).

After reconstitution the solution contains 1 mg/ml remifentanil (as hydrochloride), if prepared as recommended.

The other ingredients are:

glycine; hydrochloric acid (for pH adjustment); sodium hydroxide (for pH adjustment)

### What Remifentanil looks like and contents of the pack

Remifentanil 1/ 2/ 5 mg is a lyophilized white to slightly yellow cake or powdery mass for concentrate for solution for injection/infusion.

Each carton of Remifentanil 1 mg contains 5 vials of 3.5 ml.

Each carton of Remifentanil 2 mg contains 5 vials of 3.5 ml.

Each carton of Remifentanil 5 mg contains 5 vials of 8 ml.

## Marketing Authorisation Holder and Manufacturer

Hospira UK Limited, Horizon, Honey Lane, Hurley, Maidenhead, SL6 6RJ, UK

### Manufacturer

Elaiapharm, 2881 route des Crêtes, Z.I. Les Bouillides, Sophia Antipolis, 06560 Valbonne, France

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The following information is intended for medical or healthcare professionals only:

For detailed information please also refer to the Summary of Product Characteristics for [invented name].

## 1. Posology and method of administration

[Invented name] should only be administered in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the possible undesirable effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

Continuous infusions of [Invented name] must be administered by a calibrated infusion device into a fast flowing IV line or via a dedicated IV line. This infusion line should be connected at, or close to, the venous cannula and pre-filled to minimise the potential dead space (see section 9).

[Invented name] may also be given by target-controlled infusion (TCI) with an approved infusion device incorporating the Minto pharmacokinetic model with covariates for age and lean body mass (LBM)

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual [Invented name] after use (see section 3). [Invented name] is for intravenous use only and must not be administered by epidural or intrathecal injection (see section 2).

### 1.1 Dilution

[Invented name] must be diluted further after reconstitution. For instructions on dilution of the medicinal product before administration, see section 9.

For manually-controlled infusion [Invented name] can be diluted to concentrations of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml for paediatric patients aged 1 year and over).

For TCI the recommended dilution of [Invented name] is 20 to 50 micrograms/ml.

### 1.2 General Anaesthesia

The administration of [Invented name] must be individualised based on the patient's response.

#### 1.2.1 Adults

##### 1.2.1.1 Administration by manually-controlled infusion (MCI)

The following table summarises the initial amounts for injection/infusion and the dose range.

Table 1: Dosing guidelines for adult

Indication	REMIFENTANIL BOLUS INJECTION  (micrograms/kg)	CONTINUOUS REMIFENTANIL INFUSION  (micrograms/kg/min)	
		Initial rate	Range
Induction of anaesthesia	1 (over at least 30 seconds)	0.5 to 1	–
Maintenance of anaesthesia in ventilated patients			
• Nitrous oxide (66 %)	0.5 to 1	0.4	0.1 to 2
• Isoflurane (starting dose)	0.5 to 1	0.25	0.05 to 2

0.5 MAC) • Propofol (Starting dose 100 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2
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When given by slow bolus injection at induction [Invented name] should be administered over not less than 30 seconds.

At the doses recommended above, [Invented name] significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects (such as hypotension and bradycardia).(see *Concomitant medication*, below)

Insufficient data are available for dosage recommendations for simultaneous use of [Invented name] with hypnotics other than those listed in the Table 1.

### **Induction of anaesthesia**

[Invented name] should be co-administered with a standard dose of a hypnotic agent, such as propofol, thiopental, or isoflurane, for the induction of anaesthesia. [Invented name] can be administered at an infusion rate of 0.5 to 1 micrograms/kg/min, with or without an initial bolus injection of 1 microgram/kg given slowly over not less than 30 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the infusion of [Invented name], then a bolus injection is not necessary.

### **Maintenance of anaesthesia in ventilated patients**

After endotracheal intubation, the infusion rate of [Invented name] should be decreased, according to anaesthetic technique, as indicated in the Table 1. Due to the fast onset and short duration of action of [Invented name], the rate of administration during anaesthesia can be titrated upward in 25% to 100% increments or downward in 25% to 50% decrements, every 2 to 5 minutes to attain the desired level of  $\mu$ -opioid receptor response. In response to light anaesthesia, supplemental slow bolus injections may be administered every 2 to 5 minutes.

### **Anaesthesia in spontaneously breathing anaesthetised patients with a secured airway (e.g. laryngeal mask anaesthesia):**

In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended initial infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04 micrograms/kg/min with titration according to individual response. A range of infusion rates from 0.025 to 0.1 micrograms/kg/min has been studied.

Bolus injections are not recommended in spontaneously breathing anaesthetised patients.

[Invented name] should not be used as an analgesic in procedures where patients remain conscious or do not receive any airway support during the procedure.

### **Concomitant medication**

Remifentanyl decreases the amounts or doses of inhalational anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4).

Doses of the following agents used in anaesthesia have been reduced by up to 75 % when used concurrently with remifentanyl: isoflurane, thiopental, propofol and temazepam.

### **Guidelines for discontinuation/continuation during immediate post-operative period**

Due to the rapid offset of action of [Invented name] no residual opioid activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, other analgesics should be administered prior to discontinuation of [Invented name]. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care.

In the event that the longer-acting analgesic has not reached the appropriate effect before the end of surgery, the administration of [Invented name] can be continued to maintain analgesia during the immediate post-operative period until the longer-acting analgesic has reached the maximum effect.

Information about the administration in mechanically ventilated intensive care patients is given in section 1.4: *Use in the intensive care unit*.

In spontaneously breathing patients the initial infusion rate of [Invented name] may be decreased to 0.1 micrograms/kg/min and thereafter can be increased or decreased every 5 min in steps of 0.025 micrograms/kg/min to balance the extent of analgesia against the degree of respiratory depression.

If [Invented name] is continued post-procedural, it should only be used in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, under the close supervision of persons specifically trained in the recognition and management of the respiratory effects of potent opioids.

**Bolus injections of [Invented name] are not recommended for pain relief in patients who are spontaneously breathing during the post-operative period.**

### **1.2.1.2 Administration by target-controlled infusion (TCI)**

#### **Induction and maintenance of anaesthesia in ventilated patients**

Remifentanil TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 1 above for manually controlled infusion). In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanil concentrations ranging from 3 to 8 nanograms/ml. [Invented name] should be titrated according to individual response. For particularly painful surgical procedures target blood concentrations up to 15 nanograms/ml may be required.

At the doses recommended above, [Invented name] significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended to avoid an increase of haemodynamic effects (such as hypotension and bradycardia) (see Table 1 and *Concomitant medication* above for manually controlled infusion).

For information on blood remifentanil concentrations during TCI that correspond with various manually controlled infusion rates at steady state, see the Summary of Product Characteristics (section 6.6, Table 12).

As there are insufficient data, the administration of [Invented name] by TCI is not recommended for spontaneous ventilation anaesthesia.

#### **Guidelines for discontinuation/continuation during the immediate post-operative period**

At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 nanograms/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer-acting analgesics (see *Guidelines for discontinuation / continuation during immediate post-operative period* under *Administration by manually-controlled infusion* in section 1.2.1.1).

As there are insufficient data, the administration of [Invented name] by TCI for the management of post-operative analgesia is not recommended.

### **1.2.2 Paediatric patients (1 to 12 years of age)**

Co-administration of [Invented name] and an intravenous anaesthetic agent for induction of anaesthesia has not been studied in detail and is therefore not recommended.

[Invented name] TCI has not been studied in paediatric patients and therefore administration of [Invented name] by TCI is not recommended in these patients.

### 1.2.2.1 Maintenance of anaesthesia

The following doses of [Invented name] are recommended for maintenance of anaesthesia:

Table 2: Dosing guidelines for paediatric patients (1 to 12 years of age)

Maintenance volatile anaesthetic agent  (co-administered with nitrous oxide/oxygen in a ratio of 2:1)	Remifentanil bolus injection  (micrograms/kg)	Continuous remifentanil infusion (micrograms/kg/min)	
		Initial rate	Range for maintenance of analgesia
Halothane (starting dose 0.3 MAC)	1	0.25	0.05 to 1.3
Sevoflurane (starting dose 0.3 MAC)	1	0.25	0.05 to 0.9
Isoflurane (starting dose 0.5 MAC)	1	0.25	0.06 to 0.9

When given by bolus injection, [Invented name] should be administered over not less than 30 seconds. If a bolus dose is not given, surgery should not commence until at least 5 minutes after the start of the [Invented name] infusion.

For administration of only nitrous oxide (70%) with [Invented name], typical maintenance infusion rates should be between 0.4 and 3 micrograms/kg/min, and although not specifically studied, adult data suggest that 0.4 micrograms/kg/min is an appropriate initial rate.

Paediatric patients should be monitored carefully and the dose titrated to the depth of analgesia appropriate for the surgical procedure.

### 1.2.2.2 Concomitant medication

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane should be administered as recommended above to avoid an increase of haemodynamic effects (such as hypotension and bradycardia). Insufficient data are available for dosage recommendations for simultaneous use of remifentanil with hypnotics other than those listed in Table 2 (also see section 1.2.1.1: *Adults/Administration by manually-controlled infusion – Concomitant medication*).

### 1.2.2.3 Guidelines for patient management in the immediate post-operative period

#### Establishment of alternative analgesia prior to discontinuation of [Invented name]

Due to the rapid offset of action of [Invented name], no residual activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, other analgesics should be administered prior to discontinuation of [Invented name]. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of analgesic, the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient's surgical procedure and the level of post-operative care anticipated (see section 3).

### 1.2.3 Neonates/infants (aged less than 1 year)

There is limited clinical trial experience of remifentanil in neonates and infants (aged under 1 year old). The pharmacokinetic profile of remifentanil in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction for body weight differences. However, because there are insufficient clinical data, the administration of [Invented name] is not recommended for this age group.

#### 1.2.3.1 Use for total intravenous anaesthesia (TIVA)

There is limited clinical trial experience of remifentanil for TIVA in infants. However, there are insufficient clinical data to make dosage recommendations.

### 1.3 Use in cardiac surgery

#### 1.3.1 Administration by manually-controlled infusion

Table 3: Dosing guidelines for administration in cardiac surgery

Indication	Remifentanil bolus injection (micrograms/kg)	Continuous remifentanil infusion (micrograms/kg/min)	
		Initial rate	Typical infusion ranges
Intubation	Not recommended	1	-
Maintenance of anaesthesia			
• Isoflurane (starting dose 0.4 MAC)	0.5 to 1	1	0.003 to 4
• Propofol (Starting dose 50 micrograms/kg/min)	0.5 to 1	1	0.01 to 4.3
Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

##### 1.3.1.1 Induction of anaesthesia

After administration of hypnotic to achieve loss of consciousness, [Invented name] should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus injections of [Invented name] during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 5 minutes after the start of the infusion.

##### 1.3.1.2 Maintenance period of anaesthesia

After endotracheal intubation, the infusion rate of [Invented name] should be titrated according to the patient's need. Supplemental slow bolus doses may also be administered as required. High-risk cardiac patients, such as those undergoing valve surgery or with poor left ventricular function, should only be administered a maximum bolus dose of 0.5 micrograms/kg.

These dosing recommendations also apply during hypothermic cardiopulmonary bypass.

##### 1.3.1.3 Concomitant medication

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects (such as hypotension and bradycardia). Insufficient data are available for dosage recommendations for simultaneous use of remifentanil with hypnotics other than those listed in Table 3 (also see section 1.2.1.1: *Adults/Administration by manually-controlled infusion – Concomitant medication*).

##### 1.3.1.4 Guidelines for the post-operative care of patients

###### Continuation of [Invented name] post-operatively to provide analgesia prior to extubation

It is recommended that the infusion of [Invented name] is maintained at the final intra-operative rate during transfer of patients to the post-operative care area. The patient's level of analgesia and sedation should be closely monitored and the [Invented name] infusion rate adjusted to meet the individual patient's requirements (see section 1.4 for further information on management of intensive care patients).

###### Establishment of alternative analgesia prior to discontinuation of [Invented name]

Due to the rapid offset of action of [Invented name], no residual opioid activity will be present within 5 to 10 minutes after discontinuation. Prior to discontinuation of [Invented name], patients must be given other analgesics and sedatives sufficiently in advance to allow their therapeutic effects to become established. It is therefore important that the choice of agent(s), and the dose and the time of administration, are planned before the patient is extubated.

#### **Guidelines for discontinuation of [Invented name]**

Due to the rapid offset of action of [Invented name], hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of [Invented name]. To minimise the risk of these events, adequate alternative analgesia must be established (as described above), before the [Invented name] infusion is discontinued. The infusion rate should be reduced by 25% decrements in at least 10-minute intervals until the infusion is discontinued.

During weaning from the ventilator the [Invented name] infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics. Haemodynamic changes such as hypertension and tachycardia should be treated with other medicinal products as appropriate.

**When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.**

### **1.3.2 Administration by target-controlled infusion**

#### **1.3.2.1 Induction and maintenance of anaesthesia in ventilated patients**

[Invented name] TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 3 in section 1.3.1 above). In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil according to individual response, blood concentrations as high as 20 nanograms/ml have been achieved in clinical studies.

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects (such as hypotension and bradycardia)(see Table 3 and *Concomitant medication* in section 1.3.1).

For information on blood remifentanil concentrations achieved with manually-controlled infusion see Summary of Product Characteristics (section 6.6, Table 12).

#### **1.3.2.2 Guidelines for discontinuation/continuation during the immediate post-operative period**

At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the range of 1 to 2 nanograms/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer-acting analgesics (see *Guidelines for discontinuation of [Invented name]* under section 1.3.1.4 above).

As there are insufficient data, the administration of [Invented name] by TCI for the management of post-operative analgesia is not recommended.

### **1.3.3 Paediatric population (1 to 12 years of age)**

Data on administration in cardiac surgery are insufficient to be able to make any dosage recommendations.

## **1.4 Use in the intensive care unit (ICU)**

## 1.4.1 Adults

### 1.4.1.1 Provision of analgesia in mechanically-ventilated patients

[Invented name] can be used for the provision of analgesia in mechanically-ventilated intensive care patients. If required, additional sedating drugs should be administered.

Remifentanyl has been studied in mechanically-ventilated intensive care patients in well controlled clinical trials for up to three days. As patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore, usage of [Invented name] for longer than three days is not recommended.

Due to the lack of data on the administration of remifentanyl by TCI in ICU patients, administration of [Invented name] by TCI is not recommended for ICU patients.

In adults, it is recommended that [Invented name] is initiated at an infusion rate of 0.1 micrograms/kg/min (6 micrograms/kg/h) to 0.15 micrograms/kg/min (9 micrograms/kg/h). The infusion rate should be titrated in increments of 0.025 micrograms/kg/min (1.5 micrograms/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The patient should be monitored regularly and the [Invented name] infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min (12 micrograms/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative is initiated (see below). The dose of the sedative should be titrated to obtain the desired level of sedation. Further increases to the [Invented name] infusion rate in increments of 0.025 micrograms/kg/min (1.5 micrograms/kg/h) may be made if additional analgesia is required.

The following table summarises the initial infusion rates and typical dose range for provision of analgesia in individual patients:

Table 4: Dosing guidelines for use of [Invented name] within the intensive care setting

CONTINUOUS INFUSION micrograms/kg/min (micrograms/kg/h)	
Starting Rate	Range
0.1 (6) to 0.15 (9)	0.006 (0.38) to 0.74 (44.6)

Bolus doses of [Invented name] are not recommended in the intensive care setting.

The use of [Invented name] will reduce the dosage requirement of any concomitant sedatives. Typical starting doses for sedatives, if required, are given in Table 5.

Table 5: Recommended starting dose of sedatives, if required

Sedative Agent	Bolus (mg/kg)	Infusion rate (mg/kg/h)
Propofol	Up to 0.5	0.5
Midazolam	Up to 0.03	0.03

To allow separate titration of the respective agents, sedatives should not be administered as an admixture via the same infusion set.

### 1.4.1.2 Increasing the analgesia for ventilated patients undergoing painful procedures

An increase in the existing [Invented name] infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that a [Invented name] infusion rate of at least 0.1 micrograms/kg/min (6 micrograms/kg/h) is maintained for at least 5 minutes prior to the start of the painful procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25%-50% in anticipation of, or in response to, additional requirements for analgesia. A mean infusion rate of 0.25 micrograms/kg/min (15 micrograms/kg/h), maximum

0.74 micrograms/kg/min (45 micrograms/kg/h), has been administered for provision of additional analgesia during painful procedures.

#### **1.4.1.3 Establishment of alternative analgesia prior to discontinuation of [Invented name]**

Due to the rapid offset of action of [Invented name], no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. After administration of [Invented name] the potential for the development of tolerance and hyperalgesia should be considered. Therefore, prior to discontinuation of [Invented name], patients must be given alternative analgesics and sedatives sufficiently in advance to allow their therapeutic effects to become established and to prevent hyperalgesia and concomitant haemodynamic changes. Long-acting oral analgesics or intravenous or local analgesics, which can be controlled by the healthcare staff or the patient are alternative options for analgesia and should be titrated carefully according to the patient's needs as the dose of [Invented name] is reduced. It is recommended that the choice of agent(s), and the dose and the time of administration, are planned prior to discontinuation of [Invented name].

Prolonged administration of  $\mu$ -opioid agonists may induce development of tolerance.

#### **1.4.1.4 Guidelines for extubation and discontinuation of [Invented name]**

In order to ensure a smooth emergence from a remifentanil-based regimen it is recommended that the infusion rate of [Invented name] is titrated gradually to 0.1 micrograms/kg/min (6 micrograms/kg/h) over a period of up to 1 hour prior to extubation.

Following extubation, the infusion rate should be reduced by 25% decrements in at least 10-minute intervals until the infusion is discontinued. During weaning from the ventilator the [Invented name] infusion rate should not be increased and only down-titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of [Invented name], the IV cannula should be cleared or removed to prevent subsequent inadvertent administration.

**When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing adequate analgesia must always be balanced against the potential risk of respiratory depression.**

### **1.4.2 Intensive Care - Paediatric patients**

The use of [Invented name] in paediatric intensive care patients cannot be recommended as there are no data available in this patient population.

#### **1.4.3 Renally-impaired intensive care patients**

No adjustments to the doses recommended above are necessary in renally-impaired patients, including those undergoing renal replacement therapy. It should, however, be considered that in patients with impaired renal function the clearance of the carboxylic acid metabolite is reduced.

## **1.5 Special patient populations**

### **1.5.1 Elderly (over 65 years of age)**

#### **1.5.1.1 General anaesthesia**

Caution should be exercised in the administration of [Invented name] in this population.

The initial starting dose of [invented name] administered to patients over 65 should be half the recommended adult dose and then titrated to the individual patient's needs, as an increased sensitivity to the pharmacodynamic effects of remifentanil has been seen in this patient population.

This dose adjustment refers to the use in all phases of the anaesthesia, including induction and maintenance, and post-operative analgesia.

Because of the increased sensitivity of elderly patients to [Invented name], when administering [Invented name] by TCI in this population the initial target concentration should be 1.5 to 4 nanograms/ml with subsequent titration according to individual response.

### **1.5.1.2 Cardiac surgery**

Reduction of initial dosage is not required (see section 1.3; *Use in cardiac surgery*).

### **1.5.1.3 Intensive care**

Reduction of initial dosage is not required (see section 1.4: *Use in the intensive care unit*).

## **1.5.2 Neurosurgery**

Limited clinical experience in patients undergoing neurosurgery has shown that no special dosage recommendations are required.

### **1.5.3 ASA III/IV patients**

#### **1.5.3.1 General anaesthesia**

As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised when administering [Invented name] in this population. Initial dosage reduction and subsequent titration according to individual response is therefore recommended.

As there are insufficient data, dosage recommendation cannot be given for children.

For TCI, a lower initial target of 1.5 to 4 nanograms/ml should be used in ASA III or IV patients and subsequently titrated according to individual response.

#### **1.5.3.1 Cardiac surgery**

No initial dose reduction is required (see section 1.3: *Use in cardiac surgery*).

## **1.5.4 Obese patients**

For manually-controlled infusion it is recommended that for obese patients the dosage of [Invented name] should be based upon ideal body weight as the clearance and volume of distribution of remifentanyl are better correlated with ideal body weight than actual body weight.

With the calculation of lean body mass (LBM) used in the Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m<sup>2</sup> and in male patients with a BMI greater than 40 kg/m<sup>2</sup>. To avoid underdosing in these patients, [Invented name] by TCI should be titrated carefully according to individual response.

## **1.5.5 Renal impairment**

On the basis of investigations carried out to date, a dose adjustment in patients with impaired renal function, including intensive care patients, is not necessary

## **1.5.6 Patients with hepatic impairment**

Results from investigations to date on a limited number of patients with hepatic impairment do not justify any special dosing recommendations. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of [Invented name] (see section 3). These patients should be closely monitored and the dose of [Invented name] titrated to individual patient need.

## **2. Contraindications**

As glycine is present in the formulation, [Invented name] is contra-indicated for epidural and intrathecal use.

[Invented name] is contra-indicated in patients with known hypersensitivity to remifentanil and other fentanyl analogues or any other component of the preparation.

[Invented name] is contra-indicated for use as the sole agent for induction of anaesthesia.

### **3. Special warnings and precautions for use**

Remifentanil should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

As mechanically ventilated, intensive care patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore, a longer usage is not recommended in intensive care patients.

#### **Rapid offset of action/Switch to alternative analgesic treatment**

Due to the very rapid offset of action of remifentanil, patients may emerge rapidly from anaesthesia and no residual opioid activity will be present within 5-10 minutes after the discontinuation of remifentanil. During administration of remifentanil as a  $\mu$ -opioid agonist the potential for the development of tolerance and hyperalgesia should be paid attention to. Therefore, prior to discontinuation of remifentanil, patients must be given alternative analgesic and sedative agents at a sufficient time in advance to allow the therapeutic effects of these agents to become established and to prevent hyperalgesia and concomitant haemodynamic changes.

For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of remifentanil. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care. When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

#### **Inadvertent administration**

A sufficient amount of Remifentanil may be present in the dead space of the IV line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with IV fluids or other drugs. This may be avoided by administering [Invented name] into a fast flowing IV line or via a dedicated IV line which is removed when [Invented name] is discontinued.

#### **Discontinuation of treatment**

Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of [Invented name] in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

#### **Muscle rigidity - prevention and management**

At the doses recommended muscle rigidity may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, bolus injections should be administered over not less than 30 seconds.

Muscle rigidity induced by remifentanil must be treated in the context of the patient's clinical condition with appropriate supporting measures including ventilatory support. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a

neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of remifentanyl as an analgesic may be treated by stopping or decreasing the rate of administration of remifentanyl. Resolution of muscle rigidity after discontinuing the infusion of remifentanyl occurs within minutes. Alternatively an opioid antagonist may be administered; however this may reverse or attenuate the analgesic effect of remifentanyl.

### **Respiratory depression – preventive measures and treatment**

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, remifentanyl should only be used in areas where facilities for monitoring and dealing with respiratory depression are available. Special care should be taken in patients with impaired lung function and with severe hepatic impairment. These patients may be slightly more sensitive to the respiratory depressant effects of remifentanyl. These patients should be closely monitored and the dose of remifentanyl titrated to individual patient need.

The appearance of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50 %, or by a temporary discontinuation of the infusion. Unlike other fentanyl analogues, remifentanyl has not been shown to cause recurrent respiratory depression even after prolonged administration. However in the presence of confounding factors (e.g. inadvertent administration of bolus doses and administration of concomitant longer acting opioids), respiratory depression occurring up to 50 minutes after discontinuation of infusion has been reported. As many factors may affect post-operative recovery, it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

### **Cardiovascular effects**

Hypotension and bradycardia can give rise to asystole and cardiac arrest and may be managed by reducing the rate of infusion of remifentanyl or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolaemic, and elderly patients may be more sensitive to the cardiovascular effects of remifentanyl.

### **Neonates/infants**

There is limited data available on use in neonates/infants under 1 year of age (see section 1).

### **Drug abuse**

As with other opioids remifentanyl may produce dependency.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml.

## **4. Interaction with other medicinal products and other forms of interaction**

Remifentanyl is not metabolised by plasmacholinesterase, therefore, interactions with medicinal products metabolized by this enzyme are not anticipated.

As with other opioids remifentanyl, whether given by manually-controlled infusion or TCI, decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see section 1). If doses of concomitantly administered CNS depressant medicinal products are not reduced patients may experience an increased incidence of adverse effects associated with these agents.

Information of drug interactions with other opioids in relation to anaesthesia is very limited.

The cardiovascular effects of remifentanil (hypotension and bradycardia), may exacerbate in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents (see also section 3).

## **5. Fertility, pregnancy and lactation**

### Pregnancy

There are no adequate and well-controlled studies in pregnant women. /.../should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### Breast-feeding

It is not known whether remifentanil is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanil-related material was found in rat milk after dosing with remifentanil, nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of remifentanil.

### Labour and delivery

There are insufficient data to recommend remifentanil for use during labour and caesarean section. It is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

## **6. Overdose**

As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil. Due to the very short duration of action of remifentanil, the potential for deleterious effects due to overdose is limited to the immediate time period following medicinal product administration. Response to discontinuation of the medicinal product is rapid, with return to baseline within ten minutes.

In the event of overdose, or suspected overdose, take the following actions: discontinue administration of [Invented name], maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function. If depressed respiration is associated with muscle rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor agents for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote in addition to ventilatory support to manage severe respiratory depression. The duration of respiratory depression following overdose with [Invented name] is unlikely to exceed the duration of action of the opioid antagonist.

## **7. Incompatibilities**

[Invented name] must not be mixed with other medicinal products except those mentioned in section 9. It should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and glucose 50 mg/ml (5 %) solution for injection. [Invented name] should not be mixed with propofol in the same intravenous admixture solution. For compatibility when given into a running i.v. catheter, please see section 9.

Administration of [Invented name] into the same intravenous line with blood/serum/plasma is not recommended as non-specific esterase in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

[Invented name] should not be mixed with other therapeutic agents prior to administration.

## **8. Shelf life**

24 months

After reconstitution:

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After dilution:

The diluted product should be used immediately.

## 9. Instructions on use/handling

Remifentanil should be prepared for intravenous use by adding the appropriate volume (as stated in Table 6) of one of the below listed diluents to give a reconstituted solution with a concentration of approximately 1mg/ml.

Table 6: Volumes needed to reconstitute different vials of Remifentanil

Presentation	Volume of diluent to be added	Concentration of the reconstituted solution
Remifentanil 1 mg	1 ml	1 mg/ml
Remifentanil 2 mg	2 ml	1 mg/ml
Remifentanil 5 mg	5 ml	1 mg/ml

Following reconstitution, the product must be inspected visually (as far as supported by the vial) for solids, discoloration or damage to the vials. If such changes are detected, the solution must be discarded. The finished solution is for single use only. Unused solution must be discarded.

For manually-controlled infusion (MCI), Remifentanil should only be administered following further dilution to a concentration of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml for paediatric patients aged 1 year and over).

For target controlled infusion (TCI), Remifentanil should be administered following further dilution to a concentration of 20 to 50 micrograms/ml.

Dilution should be adjusted to the technical capability of the infusion system and the expected patient requirements.

For dilution, one of the following IV fluids listed below should be used:

Water for Injections

Glucose 50 mg/ml (5%) solution for Injection

Glucose 50 mg/ml (5%) and sodium chloride 9 mg/ml (0.9%) solution for injection

Sodium chloride 9 mg/ml (0.9%) solution for injection

Sodium chloride 4.5 mg/ml (0.45%) solution for injection

Remifentanil has been shown to be compatible with the following IV fluids when administered into a running IV catheter:

Lactated Ringer's solution for injection

Lactated Ringer's and Glucose 50 mg/ml (5%) solution for injection

Remifentanil has been shown to be compatible with propofol when administered into a running IV catheter.

Any unused product or waste material should be disposed of in accordance with local requirements.