

Remifentanyl BioAvenir

1. NAME OF THE MEDICINAL PRODUCT

Remifentanyl BioAvenir 1 mg powder for solution for injection
Remifentanyl BioAvenir 2 mg powder for solution for injection
Remifentanyl BioAvenir 5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1-mg vial: each vial contains 1 mg of Remifentanyl (as hydrochloride)
2-mg vial: each vial contains 2 mg of Remifentanyl (as hydrochloride)
5-mg vial: each vial contains 5 mg of Remifentanyl (as hydrochloride)
When reconstituted as directed, solutions of Remifentanyl for injection are clear and colourless and contain 1 mg/ml of Remifentanyl base as Remifentanyl hydrochloride.
Remifentanyl for injection is available as glass vials containing 1 mg, 2 mg or 5 mg of Remifentanyl base.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for IV injection
White to off-white, lyophilized powder, to be reconstituted before use
pH of reconstituted solution: from 2.5 to 3.5.

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see section 4.4 and 4.5).
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

4. CLINICAL DATA

4.1. Therapeutic indications

Remifentanyl BioAvenir is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia under close supervision.
Remifentanyl BioAvenir is indicated for provision of analgesia and sedation in mechanically ventilated intensive care patients 18 years of age and over.

4.2. Posology and method of administration

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 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.
Continuous infusions of Remifentanyl 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 primed to minimize the potential dead space (see section 6.6).
Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Remifentanyl after use (see section 4.4).
Remifentanyl is for intravenous (IV) use only and must not be administered by epidural or intrathecal injection (see section 4.3).

Dilution

Remifentanyl may be further diluted after reconstitution (see section 6.3 and 6.6 for storage conditions of the reconstituted/diluted product and the recommended diluents).

Administration by Manually-Controlled Infusion

For manually-controlled infusion Remifentanyl can be diluted to concentrations of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults).

General Anaesthesia

The administration of Remifentanyl must be individualized based on the patient's response. It is not recommended for use as the sole agent in general anaesthesia.

Adults

Administration by Manually-Controlled Infusion

The following table summarises the starting infusion rates and dose range:

Dosing Guidelines for Adults

Indication	Bolus Infusion (micrograms/kg)	Continuous Infusion (micrograms/kg/min)	
		Starting rate	Range
Induction of anaesthesia in ventilated patients	1 (over not less than 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
Isflurane (starting dose 0.5MAC)	0.5 to 1	0.25	0.05 to 2
Propofol (starting dose 100 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2

When given by bolus infusion at induction Remifentanyl should be administered over not less than 30 seconds.
At the doses recommended above, Remifentanyl significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia, an increase of haemodynamic effects such as hypotension and bradycardia (see Concomitant treatment).
No data are available for dosage recommendations for simultaneous use of other hypnotics with Remifentanyl.

Induction of anaesthesia: Remifentanyl should be administered with a standard dose of a hypnotic agent, such as propofol, thiopental, thiopentone or isoflurane, for the induction of anaesthesia.

Administering Remifentanyl after a hypnotic agent will reduce the incidence of muscle rigidity. Remifentanyl can be administered at an infusion rate of 0.5 to 1 micrograms/kg/min with or without an initial slow bolus infusion of 1 microgram/kg given 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 Remifentanyl, then a bolus infusion is not necessary.

Maintenance of anaesthesia in ventilated patients: After endotracheal intubation, the infusion rate of Remifentanyl should be decreased, according to anaesthetic technique, as indicated in the above table.
Due to the fast onset and short duration of action of Remifentanyl, 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 response. In response to light anaesthesia, supplemental slow bolus infusions 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. Adequate facilities should be available to monitor patients receiving Remifentanyl. It is necessary that such facilities be fully equipped to treat all degrees of respiratory depression including intubation and/or muscle rigidity (see section 4.4).

The recommended starting infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04 micrograms/kg/min with titration to effect. 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.

Remifentanyl 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 inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).
Doses of the following agents used in anaesthesia, isoflurane, thiopentone, propofol, and temazepam, have been reduced by up to 75% when used concurrently with Remifentanyl.

Guidelines for discontinuation/continuation into the immediate post-operative period: Due to the very rapid offset of action of Remifentanyl, 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, analgesics should be administered prior to or immediately following discontinuation of Remifentanyl. 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.
Care should be taken to avoid inadvertent administration of Remifentanyl remaining in IV lines and cannulae (see section 4.4).

In the event that longer acting analgesia has not been established prior to the end of surgery, Remifentanyl may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.
In ventilated patients, the infusion rate should continue to be titrated to effect.
Guidance on provision of analgesia and sedation in mechanically ventilated intensive care patients is provided below.

In patients who are breathing spontaneously, the infusion rate of Remifentanyl should initially be decreased to a rate of 0.1 micrograms/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025 micrograms/kg/min every five min, to balance the patient's level of analgesia and respiratory rate. Remifentanyl 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.
The use of bolus injections of Remifentanyl to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

Paediatric patients (2 to 12 years of age)

Induction of anaesthesia: There are insufficient data to make a dosage recommendation.

CARDIAC ANAESTHESIA

Adults

Administration by Manually-Controlled Infusion

DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

INDICATION	BOLUS INFUSION OF REMIFENTANIL (micrograms/kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/kg/min)	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	—
Maintenance of anaesthesia in ventilated patients			
· Isoflurane (starting dose 0.4MAC)	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

Remifentanyl is not recommended in patients presenting poor left ventricular function (ventricular ejection fraction of less than 0.35), because of the safety of use of this product in that patient group has not been established.

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, Remifentanyl should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus infusions of Remifentanyl during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 5 min after the start of the infusion.

Maintenance period of anaesthesia: After endotracheal intubation, the infusion rate of Remifentanyl can be titrated upward in 25% to 100% increments, or downward in 25% to 50% decrements, every 2 to 5 minutes, according to patient need. Supplemental slow bolus doses, administered over not less than 30 seconds, may also be given every 2 to 5 minutes as required. High-risk cardiac patients, such as those with poor ventricular function or undergoing valve surgery, should be administered a maximum bolus dose of 0.5 micrograms/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see section 5.2).

Concomitant medication: At the doses recommended above, Remifentanyl significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with Remifentanyl (see *Posology and Method of Administration, Adults – Concomitant medication*).

Guidelines for post-operative patient management

Guidelines for Remifentanyl post-operatively to provide analgesia prior to weaning from intubation: It is recommended that the infusion of Remifentanyl should be maintained at the final microgramic rate during transfer of patients to the post-operative care area. Upon arrival into this area, the patient's level of analgesia and sedation should be closely monitored and the Remifentanyl infusion rate adjusted to meet the individual patient's requirements.

Establishment of alternative analgesia prior to discontinuation of Remifentanyl:

Due to the very rapid offset of action of Remifentanyl, no residual opioid activity will be present within 5 to 10 minutes after discontinuation.

Prior to discontinuation of Remifentanyl, 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. It is therefore recommended that the choice of agent(s), the dose and the time of administration are planned, before weaning the patient from the ventilator.

Guidelines for discontinuation of Remifentanyl: Due to the very rapid offset of action of Remifentanyl, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of Remifentanyl. It is recommended that the risk of these occurring, adequate alternative analgesia must be established (as described above), before the Remifentanyl infusion is discontinued by reducing the infusion rate by 25% decrements in at least 10 min intervals until the infusion is discontinued. During weaning from the ventilator, the Remifentanyl infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.
It is recommended that haemodynamic changes such as hypertension and tachycardia should be treated with alternative agents 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.

Paediatric patients

There are insufficient data to make a dosage recommendation for use during cardiac surgery.

USE IN INTENSIVE CARE

Adults

Remifentanyl can be initially used alone for the provision of analgesia and sedation in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.
Remifentanyl has been studied in intensive care patients in well controlled clinical trials for up to three days. There are limited additional clinical trial data for longer durations. Therefore, the use of Remifentanyl is not recommended for a duration of treatment greater than 3 days.

In adults it is recommended that Remifentanyl is initiated at an infusion rate of 0.1 micrograms/kg/min to 0.15 micrograms/kg/min. The infusion rate should be titrated in increments of 0.025 micrograms/kg/min to achieve the desired level of analgesia and sedation. A period of at least 5 min should be allowed between dose adjustments. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the Remifentanyl infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent is initiated. The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the Remifentanyl infusion rate in increments of 0.025 micrograms/kg/min may be made if additional analgesia is required.
The following table summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients:

DOSING GUIDELINES FOR USE OF REMIFENTANIL WITHIN THE INTENSIVE CARE SETTING

CONTINUOUS INFUSION micrograms/kg/min	
Starting Rate	Range
0.1 to 0.15	0.006 to 0.74

Bolus doses of Remifentanyl are not recommended in the intensive care setting.

The use of Remifentanyl will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given below:

RECOMMENDED STARTING DOSE OF SEDATIVE AGENTS, IF REQUIRED

Sedative Agents	Bolus (mg/kg)	Infusion (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 sedative agents should not be prepared as one mixture in the same infusion bag.

Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the starting 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 Remifentanyl infusion rate of at least 0.1 micrograms/kg/min should be maintained for at least 5 min prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 min in increments of 25% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min, maximum 0.75 micrograms/kg/min, has been administered for provision of additional analgesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of Remifentanyl: Due to the very rapid offset of action of Remifentanyl, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Following administration of Remifentanyl, the possibility of tolerance and hyperalgesia should be considered. Therefore, prior to discontinuation of Remifentanyl, patients must be given alternative analgesic and sedative agents to prevent hyperalgesia and associated haemodynamic changes. These agents must be given at a sufficient time in advance to allow the therapeutic effects of these agents to become established. The range of options for analgesia includes long acting oral, intravenous, or regional analgesics controlled by the nurse or the patient. These techniques should always be titrated to individual patient needs as the infusion of Remifentanyl is reduced. It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to discontinuation of Remifentanyl.
There is a potential for the development of tolerance with time during prolonged administration of mu-opioid agonists.

Guidelines for extubation and discontinuation: Prior to discontinuation of Remifentanyl, patients must be given alternative analgesic and sedative agents at a sufficient time in advance. The appropriate choice and dose of agent(s) should be anticipated and implemented.

In order to ensure a smooth emergence from a Remifentanyl-based regimen it is recommended that the infusion rate of Remifentanyl is titrated in stages to 0.1 micrograms/kg/min over a period up to 1 hour prior to extubation. Following extubation, the infusion rate should be reduced by 25% decrements in at least 10 min intervals until the infusion is discontinued. During weaning from the ventilator the Remifentanyl infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.
Upon discontinuation of Remifentanyl the intravenous cannula should be washed or even removed to prevent subsequent inadvertent administration of the drug.

When other opioids 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.

Paediatric intensive care patients

The use of remifentanyl in intensive care patients under the age of 18 years is not recommended as there are no data available in this patient population.

Renally-impaired intensive care patients

No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy. However the clearance of the carboxylic acid metabolite is reduced in patients with renal impairment (see section 5.2).

Special patient populations

Elderly (over 65 years of age)

General anaesthesia: The initial starting dose of Remifentanyl administered to patients over 65 should be half the recommended adult dose and then shall be titrated to individual patient need as an increased sensitivity to the pharmacological effects of Remifentanyl has been seen in this patient population. This dose adjustment applies to use in all phases of anaesthesia including induction, maintenance, and immediate post-operative analgesia.

Cardiac anaesthesia: No initial dose reduction is required (see *Posology and Method of Administration, Cardiac Anaesthesia – Dosing Guidelines*).

Administration by Manually-Controlled Infusion

Intensive Care: No initial dose reduction is required (see *Posology and Method of Administration, Use in Intensive Care*).

Obese patients

For manually controlled infusion, it is recommended that for obese patients the dosage of Remifentanyl should be reduced and 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 in this population.

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

Hepatic impairment

Studies carried out with a limited number of patients with impaired liver function, do not justify any special dosage recommendations. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of Remifentanyl (see section 4.4).
These patients should be closely monitored and the dose of Remifentanyl titrated to individual patient need.

Neurosurgery

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

Patients in ASA groups III/IV

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 in the administration of Remifentanyl in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

In paediatric patients, there are insufficient data to make a dosage recommendation.

Cardiac anaesthesia: No initial dose reduction is required (see *Posology and Method of Administration, Cardiac Anaesthesia dosing guideline section*).

4.3. Contraindications

As glycine is present in the formulation, Remifentanyl for injection is contra-indicated for epidural and intrathecal use (see section 5.3).

Remifentanyl is contra-indicated in patients with known hypersensitivity to any component of the preparation and other fentanyl analogues, or to any of the excipients listed in section 6.1.

The use of Remifentanyl as the sole agent for the induction of anaesthesia is contraindicated.

Children under 2 years of age.

4.4. Warnings and special precautions for use

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 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 with all opioids, Remifentanyl is not recommended for use as the sole agent in general anaesthesia.

Remifentanyl is not recommended for use in mechanically-ventilated patients hospitalized in Intensive Care Units undergoing treatments for more than three days.

Patients with known hypersensitivity to opioids of a different class may exhibit a hypersensitivity reaction following administration of Remifentanyl. Caution should be exercised before using Remifentanyl in these patients.

Rapid offset of action/Transition to alternative analgesia

Due to the very rapid offset of action of Remifentanyl, no residual opioid activity will be present within 5 to 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. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit. Prior to discontinuation of Remifentanyl, patients must be given alternative analgesic and sedative agents. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), 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. 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Remifentanyl and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Remifentanyl concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Discontinuation of Treatment

Symptoms following withdrawal of Remifentanyl 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 Remifentanyl in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

Inadvertent administration

A sufficient amount of Remifentanyl 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 Remifentanyl into a fast flowing IV line or via a dedicated IV line which is removed when Remifentanyl is discontinued.

Muscle rigidity – prevention and management

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

Muscle rigidity induced by Remifentanyl 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 – prevention and management

As with all potent opioids, profound analgesia is accompanied by marked apnea respiratory depression. There are cases of patients with delayed respiratory depression 20–30 minutes after cessation of the Remifentanyl infusion. Therefore, Remifentanyl should only be used in areas where facilities for monitoring and treating respiratory depression are available. Special attention should be paid to patients with respiratory system dysfunction. The occurrence of respiratory depression should be treated appropriately, including decreasing the infusion rate by up to 50% or temporarily discontinuing the infusion. Unlike other fentanyl analogues, Remifentanyl has not been shown to cause recurrent respiratory depression even after prolonged administration. Nevertheless, given the multiplicity of factors that may affect post-operative recovery, it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient leaves the recovery area.

Cardiovascular effects

The risk of occurrence of cardiovascular effects such as hypotension and bradycardia, which rarely lead to asystole/ cardiac arrest (see section 4.5 ad 4.8), can be managed by reducing the infusion rate of Remifentanyl or the dose of the concurrent anaesthetics, or by using IV fluids, vasopressor or anticholinergic agents as appropriate.
Dehydrated, hypovolemic, hypotensive, and elderly patients may be more sensitive to the cardiovascular effects of Remifentanyl.

Drug abuse

As with other opioids, Remifentanyl may produce dependency.

4.5. Interaction with other medicinal products and other forms of interaction

Remifentanyl is not metabolized by plasma cholinesterase; therefore, interactions with drugs metabolized by this enzyme are not expected.

As with other opioids, Remifentanyl, whether given by manually-controlled infusion, decreases the amounts or doses of inhaled IV anaesthetics, and benzodiazepines required for anaesthesia (see section 4.2). If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

The cardiovascular effects of Remifentanyl (hypotension and bradycardia- see section 4.4 and 4.8), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women.

Remifentanyl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether remifentanyl is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanyl-related material was found in rat milk after dosing with remifentanyl, nursing mothers should be advised to discontinue breast feeding for 24 hours following administration of remifentanyl. For a summary of the reproductive toxicity study findings: please refer to Section 5.3 Preclinical safety data.

Labor and delivery

The safety profile of Remifentanyl during labour or delivery has not been demonstrated. There are insufficient data to recommend Remifentanyl for use during labour and caesarean section. Remifentanyl crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

4.7. Effects on the ability to drive and to use machinery

After anaesthesia with remifentanyl the patient should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely.

4.8. Adverse effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/100$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($> 1/10,000$ and $< 1/1,000$) and very rare ($< 1/10,000$).

Clinical Trial Data

The most common adverse events associated with Remifentanyl are direct extensions of mu-opioid agonist pharmacology. The overall reporting incidence, as determined from all phases of controlled anaesthesia studies at recommended doses, is presented below.

These adverse events resolve within minutes of discontinuing or decreasing the rate of Remifentanyl administration.

Nervous system disorders	
Very common:	Musculoskeletal rigidity
Rare:	Sedation (during recovery from general anaesthesia)
Not known:	Convulsions
Cardiac disorders	
Common:	Bradycardia
Rare:	Asystole/cardiac arrest, generally preceded by bradycardia, has been reported in patients receiving Remifentanyl together with other anaesthetic drugs.
Not known:	Atrioventricular block
Vascular disorders	
Very common:	Hypotension
Common:	Post-operative hypertension
Respiratory, thoracic, and mediastinal disorders	
Common:	Acute respiratory depression, apnea
Uncommon:	Hypoxia
Gastrointestinal disorders	
Very common:	Nausea, vomiting
Uncommon:	Constipation
Skin and subcutaneous tissue disorders	
Common:	Pruritus
General disorders and disturbance of the administration site	
Common:	Post-operative shivering
Uncommon:	Post-operative aches
Not known:	Drug tolerance
Immune system disorders	
Rare:	Allergic reactions, including anaphylaxis, have been reported in patients receiving Remifentanyl together with one or more anaesthetic drugs.
Psychiatric disorders	
Not known:	Drug dependence

Discontinuation of treatment

Symptoms following withdrawal of remifentanyl including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov/ll/>

4.9. Overdose

Symptoms

As with all potent opioid analgesics, an overdose would be manifested by an extension of the pharmacologically-predictable actions of Remifentanyl.

Due to the very short duration of action of Remifentanyl the potential for deleterious effects due to overdose is limited to the immediate time period following drug administration. Response to discontinuation of the drug is rapid, with return to baseline within ten minutes.

Management

In case of an overdose or suspected overdose, take the following actions: discontinue administration of Remifentanyl, maintain an open airway, initiate assisted or controlled ventilation with oxygen, and maintain an adequate cardiovascular function. If respiratory depression is associated with muscle rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor agents for 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 and muscle rigidity. The duration of respiratory depression following overdose with Remifentanyl is unlikely to exceed the duration of action of the opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: opioid anaesthetics, ATC code: N01A H06.

Remifentanyl is a selective μ -opioid agonist with rapid onset and very short duration of action. The μ -opioid activity of Remifentanyl is antagonized by narcotic antagonists such as naloxone.

Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after bolus administration of Remifentanyl in doses of up to 30 micrograms/kg.

5.2. Pharmacokinetic properties

Absorption

Blood concentrations of Remifentanyl are proportional to the dose administered throughout the recommended dose range. For every 0.1 micrograms/kg/min increase in infusion rate, the blood concentration of Remifentanyl will rise 2.5 nanograms/ml.

Distribution

The central volume of distribution is 100 ml/kg, and the steady-state volume of distribution is 350 ml/kg. Remifentanyl is approximately 70% bound to plasma proteins.

Metabolism

Remifentanyl is an Esterase Metabolised Opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of Remifentanyl results in the formation of an essentially inactive carboxylic acid metabolite (114600* as potent as Remifentanyl). The half life of the metabolite in healthy adults is 2 h. Approximately 95% of Remifentanyl is recovered in the urine as the carboxylic acid metabolite. Remifentanyl is not a substrate for plasma cholinesterase.

Elimination

Following administration of the recommended doses of Remifentanyl, the effective biological half-life is 3-10 minutes. The average clearance of Remifentanyl in young healthy adults is 40ml/min/kg.

Special patients population

Cardiac anaesthesia

The clearance of Remifentanyl is reduced by approximately 20% during the hypothermic cardiopulmonary bypass (28°C). A decrease in body temperature reduces elimination clearance in the region of up to 3% per degree centigrade.

Renal impairment

The patient's renal condition does not affect his rapid recovery from Remifentanyl-based sedation and analgesia. The pharmacokinetic parameters of Remifentanyl do not vary significantly in patients with varying degrees of renal failure, even after administration by continuous infusion for up to 3 days in Intensive Care Units.

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. In intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite is expected to reach approximately 250-fold the level of Remifentanyl at steady-state. Clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant mu-opioid effects even after administration of Remifentanyl infusions for up to 3 days in these patients.

There is no evidence that Remifentanyl is excreted during renal replacement therapy. The carboxylic acid metabolite is excreted during haemodialysis by 25-35%.

Hepatic impairment

The pharmacokinetics of Remifentanyl remains unchanged in patients with severe hepatic impairment awaiting liver transplant or during the anhepatic phase of liver transplant surgery.

Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of Remifentanyl. These patients should be closely monitored and the dose of Remifentanyl should be titrated to the individual patient need.

Pediatric patients

In paediatric patients 5 days to 17 years of age, the average clearance and steady state volume of distribution of Remifentanyl are increased in younger children and decline to young healthy adult values by age 17. The half life of Remifentanyl is not significantly different in neonates suggesting that changes in analgesic effect after changes in infusion rate of Remifentanyl should be rapid and similar to that seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 to 17 years of age are similar to those seen in adults after correcting for differences in body weight.

Elderly

The clearance of Remifentanyl is slightly reduced (approximately 25%) in elderly patients (aged over 65), compared to that of young patients. The pharmacodynamic activity of Remifentanyl increases with increasing age. Elderly patients have a Remifentanyl EC50 for formation of delta waves in the electroencephalogram (EEG) that is 50% lower than young patients; therefore, the initial dose of Remifentanyl should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

Placental and milk transfer

In a human clinical trial, the concentration of Remifentanyl in fetal blood was approximately 50% of that in maternal blood. The fetal arterio-venous ratio of Remifentanyl concentrations was approximately 30% suggesting metabolism of Remifentanyl in the neonate.

5.3. Preclinical safety data

Intrathecal administration of the glycine formulation without Remifentanyl to dogs caused agitation, pain and hind limb dysfunction and in-coordination. These effects are believed to be secondary to the glycine excitant. Glycine is a commonly used excitant in intravenous products and this finding has no relevance for intravenous administration of Remifentanyl.

Remifentanyl, like other opioid agonists, produced increases in action potential duration (APD) in dog isolated Purkinje fibres. For Remifentanyl, the effects were seen at concentrations of 1 micromolar or higher (which are higher than plasma concentrations seen in clinical practice). There were no effects at a concentration of 0.1 micromolar.

The major metabolite Remifentanyl acid had no effect on APD up to the maximum tested concentration of 10 micromolar.

Remifentanyl-related material was found in rat milk after dosing with Remifentanyl. Placental transfer studies in rats and rabbits showed that pups are exposed to Remifentanyl and/or its metabolites during growth and development. There have been no additional findings of clinical relevance.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Glycine

Hydrochloric acid (for pH adjustment)

6.2. Incompatibilities

This medicament must not be mixed with others except those mentioned in section 6.6.

It should not be mixed with Lactated Ringer's injection or with Lactated Ringer's and glucose 5% (50 mg/ml) solution for injection.

Remifentanyl should not be mixed with propofol in the same intravenous mixture solution.

Administration of Remifentanyl in the same intravenous line with blood/serum/plasma is not recommended, because the presence of non-specific esterase in blood products may lead to the hydrolysis of Remifentanyl to its inactive metabolite.

Remifentanyl should not be mixed with other medicinal products prior to administration.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical stability have been demonstrated during use of the reconstituted solution for 24 hours at temperature below 25°C.

Chemical and physical stability have been demonstrated during use of the reconstituted and further diluted solutions of Remifentanyl are stable for 24 hours stored at room temperature below 25°C, if the product is diluted with: Water for injection, 5% Dextrose, 0.9% Sod. chloride injection.

Reconstituted and further diluted solutions of Remifentanyl is stable for 4 hours stored at room temperature, if the product is diluted with: Lactated Ringer's Injection and 5% Dextrose Injection. Remifentanyl does not contain an antimicrobial preservative. **Therefore from a microbiological point of view, 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 and normally would not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

1-mg 2-mg and 5-mg vials: store at temperatures below 25°C.

For storage conditions of the reconstituted and diluted medication, see section 6.3.

6.5. Nature and contents of container

3 ml vial (type-I colorless glass) of Remifentanyl 1 mg with chlorobutyl plug and flip-off capsule.

3 ml vial (type-I colorless glass) of Remifentanyl 2 mg with chlorobutyl plug and flip-off capsule.

6 ml vial (type-I colorless glass) of Remifentanyl 5 mg with chlorobutyl plug and flip-off capsule.

Packs of 5 vials.

6.6. Special precautions for disposal

To prepare Remifentanyl for intravenous administration, 1, 2, or 5 ml of the diluent should be added, as applicable, in order to obtain a reconstituted solution with a concentration of 1 mg/ml.

The reconstituted solution is clear, colorless, and practically free from particulate material.

Following reconstitution, visually inspect the product (where the container permits) for particulate material, discoloration or damage of container. Discard any solution in which such defects are detected. The reconstituted product is for single use only. Any unused material should be discarded.

Remifentanyl should not be administered via manually-controlled infusion without further dilution to concentrations of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults).

Dilution depends on the technical capacity of the infusion device and on the patient's expected requirements.

Reconstitution diluent:

1. Water for injection
2. 0.9% Sodium Chloride Injection
3. 0.45% Sodium Chloride Injection
4. 5% Dextrose Injection
5. 5% Dextrose and 0.9% Sodium Chloride Injection

Dilution fluid

1. Water for injection
2. 0.9% Sodium Chloride solution for injection
3. 0.45% Sodium Chloride solution for injection
4. 5% Dextrose solution for injection
5. 5% Dextrose and 0.9% Sodium Chloride solution for injection
6. Lactated Ringer's Injection (*)
7. Lactated Ringer's Injection and 5% Dextrose Injection (*)

(*) Firstly the product will be reconstituted with water for injection and further diluted with Lactated Ringer's Injection and Lactated Ringer's and 5% Dextrose Injection.

Following dilution, visually inspect the product to ensure that it is transparent, colorless, virtually free from solids, and that the vial is not damaged. Discard any solution in which such defects are detected.

Remifentanyl is compatible with the following intravenous fluids when administered into an intravenous catheter: - Lactated Ringer's injection

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

Remifentanyl has been shown to be compatible with propofol when administered into an intravenous catheter.

The following tables give guidelines for infusion rates of Remifentanyl for manually-controlled infusion:

Table 1 Remifentanyl for Injection Infusion Rates (ml/kg/h)

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of		
	25µg/1ml 1mg/40ml	50µg/1ml 1mg/20ml	250µg/ml 10mg/40ml
0.0125	0.03	0.015	not recommended
0.025	0.06	0.03	not recommended
0.05	0.12	0.06	0.012
0.075	0.18	0.09	0.018
0.1	0.24	0.12	0.024
0.15	0.36	0.18	0.036
0.2	0.48	0.24	0.048
0.25	0.6	0.3	0.06
0.5	1.2	0.6	0.12
0.75	1.8	0.9	0.18
1.0	2.4	1.2	0.24
1.25	3.0	1.5	0.3
1.5	3.6	1.8	0.36
1.75	4.2	2.1	0.42
2.0	4.8	2.4	0.48

Table 2 Remifentanyl for Injection Infusion Rates (ml/h) for a 20 micrograms/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)						
	5	10	20	30	40	50	60
0.0125	0.188	0.375	0.75	1.125	1.5	1.875	2.25
0.025	0.375	0.75	1.5	2.25	3.0	3.75	4.5
0.05	0.75	1.5	3.0	4.5	6.0	7.5	9.0
0.075	1.125	2.25	4.5	6.75	9.0	11.25	13.5
0.1	1.5	3.0	6.0	9.0	12.0	15.0	18.0
0.15	2.25	4.5	9.0	13.5	18.0	22.5	27.0
0.2	3.0	6.0	12.0	18.0	24.0	30.0	36.0
0.25	3.75	7.5	15.0	22.5	30.0	37.5	45.0
0.3	4.5	9.0	18.0	27.0	36.0	45.0	54.0
0.35	5.25	10.5	21.0	31.5	42.0	52.5	63.0
0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 3 Remifentanyl for Injection Infusion Rates (ml/h) for a 25 micrograms/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	10	20	30	40	50	60	70	80	90	100
0.0125	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.025	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.05	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.075	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.1	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.15	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
0.2	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4	43.2	48.0

Table 4 Remifentanyl for Injection Infusion Rates (ml/h) for a 50 micrograms/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	30	40	50	60	70	80	90	100		
0.025	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0		
0.05	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0		
0.075	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0		
0.1	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0		
0.15	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0		
0.2	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0		
0.25	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0		
0.5	18.0	24.0	30.0	36.0	42.0	48.0	54.0	60.0		
0.75	27.0	36.0	45.0	54.0	63.0	72.0	81.0	90.0		
1.0	36.0	48.0	60.0	72.0	84.0	96.0	108.0	120.0		
1.25	45.0	60.0	75.0	90.0	105.0	120.0	135.0	150.0		
1.5	54.0	72.0	90.0	108.0	126.0	144.0	162.0	180.0		
1.75	63.0	84.0	105.0	126.0	147.0	168.0	189.0	210.0		
2.0	72.0	96.0	120.0	144.0	168.0	192.0	216.0	240.0		

Table 5 Remifentanyl for Injection Infusion Rates (ml/h) for a 250 micrograms/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	30	40	50	60	70	80	90	100		
0.1	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40		
0.15	1.08	1.44	1.80	2.16	2.52	2.88	3.24	3.60		
0.2	1.44	1.92	2.40	2.88	3.36	3.84	4.32	4.80		
0.25	1.80	2.40	3.00	3.60	4.20	4.80	5			