Remifentanil BioAvenir

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1-mg vial: each vial contains 1 mg of Remifentanil (as hydrochloride)

2-mg vial: each vial contains 2 mg of Remifentanil (as hydrochloride)

5-mg vial: each vial contains 5 mg of Remifentanil (as hydrochloride)

When reconstituted as directed, solutions of Remifentanil for injection are clear and colourless and contain 1 mg/ml of Remifentanil base as Remifentanil hydrochloride.

Remifentanil for injection is available as glass vials containing 1 mg, 2 mg or 5 mg of Remifentanil base.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for i.v 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

Remifentanil Bioavenir is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia under close supervision. Remifentanil 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

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.

Continuous infusions of Remifentanil must be administered by a calibrated infusion device into a fast- flowing I.V line or via a dedicated I.V 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 Remifentanil after use (see Section 4.4).

Remifentanil is for intravenous (I.V.) use only and must not be administered by epidural or intrathecal injection (see section 4.3).

Dilution

Remifentanil 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 Remifentanil can be diluted to concentrations of 20 to 250 micrograms/ml

(50 micrograms/ml is the recommended dilution for adults).

(See sectionn 6.6)

4.2.1 General Anaesthesia

The administration of Remifentanil must be individualized based on the patient's response. Specific dosing guidelines for patients undergoing cardiac surgery are provided in section 4.2.2 below.

4.2.1.1 Adults

Administration **by Manually-Controlled Infusion**
The following table summarises the starting infusion rates and dose range:

Dosing Guidelines for Adults

Indication	**Bolus Injection (micrograms/kg)**	**Continuous Infusion (micrograms/kg/ min)**	
		Starting rate	**Range**
Induction of anaesthesia	1 (give 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
Isoflurane (starting dose 0.5MAC)	0.5 to 1	0.25	0.05 to 2
Propofol (starting dose100 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2

When given by bolus infusion at induction Remifentanil should be administered over not less than 30 seconds.
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 Concomitant treatment).

Induction of anaesthesia: Remifentanil should be adminstered with a standard dose of a hypnotic agent, such as propofol, thiopental, thiopentone or isoflurane, for the induction of anaesthesia.
Administering Remifentanil after a hypnotic agent will reduce the incidence of muscle rigidity. Remifentanil 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 Remifentanil, then a bolus injection is not necessary.

Maintenance of anaesthesia in ventilated patients: After endotracheal intubation, the infusion rate of Remifentanil should be decreased, according to anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of Remifentanil , 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 injection 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 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.

Remifentanil 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: Remifentanil 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 Remifentanil.

Guidelines for discontinuation/ Continuation into the immediate post-operative period: Due to the very rapid offset of action of Remifentanil, 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 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.

Care should be taken to avoid inadvertent administration of Remifentanil 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, Remifentanil 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 in section 4.2.3 below.
In patients who are breathing spontaneously, the infusion rate of Remifentanil 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 minutes, to balance the patient's level of analgesia and respiratory rate. Remifentanil 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 Remifentanil to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

4.2.1.2 Paediatric patients (2 to 12 years of age)

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

4.2.2 Cardiac anaesthesia

Administration **by Manually-Controlled Infusion**

DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

INDICATION	**BOLUS INJECTION 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) □ Propofol (starting dose 50 (micrograms/kg/min)	0.5 to 1 0.5 to 1	1 1	0.003 to 4 0.01 to 4.3
Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, Remifentanil should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus injection of Remifentanil 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 Remifentanil 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, Remifentanil 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 Remifentanil (see section 4.2.1.1 *Posology and Method of Administration, Adults* - Concomitant *medication*).

Guidelines for post-operative patient management

Continuation of Remifentanil post-operatively to provide analgesia prior to weaning for extubation: It is recommended that the infusion of Remifentanil should be maintained at the final intra-operative 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 Remifentanil infusion rate adjusted to meet the individual patient's requirements (see section 4.2.3 for furter information on management of intensive care patients).

Establishment of alternative analgesia prior to discontinuation of Remifentanil:

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

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. 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 Remifentanil: Due to the very rapid offset of action of Remifentanil, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of Remifentanil (see section 4.8). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the Remifentanil infusion is discontinued. The infusion rate should be reduced by 25% decrements in at least 10 minutes intervals until the infusion is discontinued. During weaning from the ventilator, the Remifentanil 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 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.

4.2.3 USE IN INTENSIVE CARE

Remifentanil can be used for the provision of analgesia in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.
Remifentanil 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, the use of of Remifentanil is not recommended for a duration of treatment greater than 3 days.
In adults it is recommended that Remifentanil 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 and sedation. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the Remifentanil 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 agent is initiated. The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the Remifentanil 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 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** (micrograms/kg/h)	
Starting Rate	**Range**
0.1 (6) to 0.15 (9)	0.006 (0.36) to 0.74 (44.4)

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

The use of Remifentanil 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 Agent	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 agent's 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 existing Remifentanil 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 Remifentanil infusion rate of at least 0.1 micrograms/kg/min (6 micrograms/kg/h) 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 minutes 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 (15 micrograms/kg/h) , maximum 0.75 micrograms/kg/min (45 micrograms/kg/h) , has been administered for provision of additional analgesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of Remifentanil:
Due to the very rapid offset of action of remifentanil, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Following administration of Remifentanil, the possibility of tolerance and hyperalgesia should be considered. Therefore, prior to discontinuation of Remifentanil, 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 Remifentanil is reduced. It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to discontinuation of Remifentanil.

There is a potential for the development of tolerance with time during prolonged administration of mu-opioid agonists.

Guidelines for extubation and discontinuation of Remifentanil:
In order to ensure a smooth emergence from a Remifentanil -based regimen it is recommended that the infusion rate of Remifentanil is titrated in stages to 0.1 micrograms/kg/min (6 micrograms/kg/h) 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 minutes intervals until the infusion is discontinued. During weaning from the ventilator the Remifentanil infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.
Upon discontinuation of Remifentanil, the intravenous (I.V)_ cannula should be cleared or 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.

4.2.3.1 Pediatric intensive care patients

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

4.2.3.2 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).

4.2.4 Special patient populations

4.2.4.1 Elderly (over 65 years of age)

General anaesthesia: The initial starting dose of Remifentanil 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 Remifentanil 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 section 4.2.2 Posology,* Cardiac Anaesthesia — Dosing guidelines).

Intensive Care: No initial dose reduction is required (*see section 4.2.3 Posology and Method of Administration,* Use in Intensive Care).

4.2.4.2 Obese patients

For manually controlled infusion, it is recommended that for obese patients the dosage of Remifentanil should be reduced and based upon ideal body weight as the clearance and volume of distribution of Remifentanil are better correlated with ideal body weight than actual body weight in this population.

4.2.4.3 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.

4.2.4.4 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 Remifentanil (*see section 4.4*).
These patients should be closely monitored and the dose of Remifentanil shall be titrated to individual patient need.

4.2.4.5 Neurosurgery

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

4.2.4.6 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 Remifentanil 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 section 4.2.2 *Posology and Method of Administration,* Cardiac Anesthesia dosing guideline section).

4.3. Contraindications

As glycine is present in the formulation, Remifentanil for injection is contra-indicated for epidural and intrathecal use (see section 5.3).
Hypersensitivity to the active substance, other fentanyl analogues, or any of the excipients listed in section 6.1.

The use of Remifentanil as the sole agent for the induction of anesthesia is contraindicated.

Childern under 2 years of age.

4.4. Warnings and special 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. The use of Remifentanil in mechanically ventilated intensive care patients is not recommended for a duration of treatment greater than 3 days.

Patients with a known hypersensitivity to opioids of a different class may exhibit a hypersensitivity reaction following administration of Remifentanil. Caution should be exercised before using Remifentanil in these patients.
Rapid offset of action /Transition to alternative analgesia
Due to the very rapid offset of action of Remifentanil, no residual opioid activity will be present within 5 to 10 minutes after the discontinuation of Remifentanil. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Remifentanil. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit. Prior to discontinuation of Remifentanil, 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 Remifentanil 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 Remifentanil 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 and withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy.

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 Remifentanil in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

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 Remifentanil into a fast flowing IV line or via a dedicated IV line which is removed when Remifentanil 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 injection 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 Remifentanil as an analgesic may be treated by stopping or decreasing the rate of administration of Remifentanil. Resolution of muscle rigidity after discontinuing the infusion of Remifentanil occurs within minutes. Alternatively an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of Remifentanil.

Respiratory depression - prevention and management
As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, Remifentanil 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 treatedappropriately, including decreasing the infusion rate by up to 50% or temporarily discontinuing the infusion. Unlike other fentanyl analogues, Remifentanil has not been shown to cause recurrent respiratory depression even after prolonged administration. However, 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
The risk of occurrence of cardiovascular effects such as hypotension and bradycardia, which may rarely lead to asystole/cardiac arrest (*see section 4.5 and 4.8*), may by reduce

by lowering the rate of infusion of Remifentanil or the dose of the concurrent anesthetics, or by using IV fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolemic, and elderly patients may be more sensitive to the cardiovascular effects of Remifentanil.

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Drug abuse

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

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

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

As with other opioids Remifentanil, whether given by manually-controlled infusion, decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (*see section 4.2* Posology and method of administration, General Anaesthesia – Adults, Paediatric Patients, and Cardiac Surgery). 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 concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death. Co-administration of remifentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Monoamine Oxidase Inhibitors (MAOIs) may increase the risk of serotonin syndrome, a potentially life-threatening condition. Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to Remifentanil use.

The cardiovascular effects of Remifentanil (hypotension and bradycardia), 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.
Remifentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.
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 Remifentanil during labour or delivery has not been demonstrated. There are insufficient data to recommend Remifentanil for use during labour and caesarean section.

Remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child. In case Remifentanil is administered nevertheless, the patient and the neonate must be monitored for signs of excess sedation or respiratory depression (*see section 4.4*).

4.7. Effects on the ability to drive and to use machinery
After anaesthesia with remifentanil 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:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely.

4.8 Undesirable effects

Summary of the safety profile

The most common undesirableeffect associated with Remifentanil are direct extensions of mu-opioid agonist pharmacology.
These adverse events resolve within minutes of discontinuing or decreasing the rate of Remifentanil administration.

Tabulated list of adverse reactionsAdverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (> 1/10,000 and < 1/1,000) and very rare (< 1/10,000).

System organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Rare	Allergic reactions, including anaphylaxis, have been reported in patients receiving Remifentanil in conjuction with one or more anaesthetic drugs.
Psychiatric disorders	Not known	Drug dependence, withdrawl syndrome
Nervous system disorders	Very common	Skeletal muscale rigidity
	Rare	Sedation (during recovery from general anesthesia)
	Not known	Convulsions
Cardiac disorders	common	Bradycardia
	Rare	Asystole/cardiac arrest, generally preceded by bradycardia, has been reported in patients receiving Remifentanil in conjuction with other anesthetic agents.
	Not known	Atrioventricular block, arrhythmia
Vascular disorders	Very common	Hypotension
	common	Post-operative hypertension
Respiratory, thoracic, and mediastinal disorders	common	Acute respiratory depression, apnoea, cough
	uncommon	Hypoxia
	Very common	Nausea, vomiting

Gastrointestinal disorders	uncommon	Constipation
Skin and subcutaneous tissue disorders	common	Pruritus
General disorders and disturbance of the administration site	common	Post-operative shivering
	ucommon	Post-operative aches
	Not known	Drug tolerance

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 (*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.il/

4.9. Overdose ,

Symptoms
As with all potent opioid analgesics, an 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 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 Remifentanil, 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 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 Remifentanil is unlikely to exceed the duration of action of the opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group:Opioid anesthetics, ATC code: N01A H06.

Remifentanil is a selective μ-opioid agonist with rapid onset and very short duration of action. The μ-opioid activity of Remifentanil 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 Remifentanil in doses of up to 30 micrograms/kg.

Neonates/infants (aged less than 1 year):
In a randomised (ratio of 2:1, remifentanil:halothane), open label, parallel group, multicentre study in 60 young infants and neonates ≤8 weeks of age (mean 5.5 weeks) with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0.4 μg/kg/min initial continuous infusion plus supplemental doses or infusion rate changes as needed) was compared with halothane (given at 0.4% with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 70% nitrous oxide (N_20) plus 30% oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant).
Use for Total Intravenous Anaesthesia (TIVA) - children aged 6 months to 16 years
TIVA with remifentanil in paediatric surgery was compared to inhalation anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical intervention	Age (y), (N)	Study condition (maintenance)	Extubation (min) (mean (SD))
Lower	0.5-16	TIVA: propofol (5 -	11.8 (4.2)

abdominal/urological surgery	(120)	10 mg/kg/h) + remifentanil (0.125 - 1.0 µg/kg/min)	
		Inhalation anaesthesia: sevoflurane (1.0 - 1.5 MAC) and remifentanil (0.125 - 1.0 µg/kg/min)	15.0 (5.6) ($p<0.05$)
ENT-surgery	4-11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0.5 µg/kg/min)	11 (3.7)
		Inhalation anaesthesia: desflurane (1.3 MAC) and N_2O mixture	9.4 (2.9) Not significant
General or ENT surgery	2-12 (153)	TIVA: remifentanil (0.2 - 0.5 µg/kg/min) + propofol (100 - 200 µg/kg/min)	Comparable extubation times (based on limited data)
		Inhalation anaesthesia: sevoflurane (1 - 1.5 MAC) + N_2O mixture	

In the study in lower abdominal/urological surgery comparing remifentanil/propofol with remifentanil/sevoflurane, hypotension occurred significantly more often under remifentanil/sevoflurane, and bradycardia occurred significantly more often under remifentanil/propofol. In the study in ENT surgery comparing remifentanil/propofol with desflurane/nitrous oxide, a significantly higher heart rate was seen in subjects receiving desflurane/nitrous oxide compared with remifentanil/propofol and with baseline values.

5.2. Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg, the central volume of distribution is 100 ml/kg and the steady-state volume of distribution is 350 ml/kg. In children aged 1 to 12 years, remifentanil clearance and volume of distribution decreases with increasing age; the values of these parameters in neonates are approximately twice those of healthy young adults.

Absorption
Blood concentrations of Remifentanil 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 Remifentanil will rise 2.5 nanograms/ml. Remifentanil is approximately 70% bound to plasm protein.

Biotransformation
Remifentanil is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite (1/4600th as potent as remifentanil). The half life of the metabolite in healthy adults is 2 hours. Approximately 95% of remifentanil is recovered in the urine as the carboxylic acid metabolite. Remifentanil is not a substrate for plasma cholinesterase.

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

Renal impairment

The rapid recovery from Remifentanil-based sedation and analgesia is unaffected by renal status.

The pharmacokinetic parameters of Remifentanil 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. Especially 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 Remifentanil at steady-state. Clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant mu-opioid effects even after administration of Remifentanil infusions for up to 3 days in these patients.

There is no evidence that Remifentanil is extracted during renal replacement therpay.

The carboxylic acid metabolite is extracted during haemodialysis by 25 - 35 %.

Hepatic impairment

The pharmacokinetics of Remifentanil 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 Remifentanil. These patients should be closely

monitored and the dose of Remifentanil should be titrated to the individual patient need.

Pediatric patients

The average clearance and steady state volume of distribution of Remifentanil are increased in younger children and decline to young healthy adult values by age 17. The elimination half life of Remifentanil in neonates is not significantly different from that of young healthy adults. Changes in analgesic effect after changes in infusion rate of Remifentanil 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 Remifentanil is slightly reduced (approximately 25%) in elderly patients (aged over 65), compared to that of young patients. The pharmacodynamic activity of Remifentanil increases with increasing age. Elderly patients have a Remifentanil EC50 for formation of delta waves in the electroencephalogram (EEG) that is 50% lower than young patients; therefore, the initial dose of Remifentanil 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 mean ratio of maternal arterial to umbilical venous concentration indicated that the neonate was exposed to approximately 50% concentration of Remifentanil to that in the mother. The mean umbilical arterio-venous ratio of Remifentanil concentrations was approximately 30% suggesting metabolism of Remifentanil in the neonate.

5.3. Preclinical safety data

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

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

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

Reproductive toxicity studies

Remifentanil has been shown to reduce fertility in male rats when administered daily by intravenous injection for at least 70 days at a dose of 0.5 mg/kg, or approximately 250 times the maximum recommended human bolus dose of 2 micrograms/kg. The fertility of female rats was not affected at doses up to 1mg/kg when administered for at least 15 days prior to mating. No teratogenic effects have been observed with remifentanil at doses up to 5 mg/kg in rats and 0.8 mg/kg in rabbits. Administration of remifentanil to rats throughout late gestation and lactation at doses up to 5 mg/kg IV had no significant effect on the survival, development, or reproductive performance of the F1 generation.

Genotoxicity

Remifentanil was devoid of genotoxic activity in bacteria and in rat liver or mouse bone marrow cells in vivo. However, a positive response was seen in vitro in different mammalian cell systems in the presence of a metabolic activation system. This activity was seen only at concentrations more than three orders of magnitude higher than therapeutic blood levels.

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.

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

Administration of Remifentanil 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 Remifentanil to its inactive metabolite.

Remifentanil 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 tempature below 25ºC.

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

Reconstituted and further diluted solutions of Remifentanil is stable for 4 hours stored at room temperature, if the product is diluted with: Lactated Ringer's Injection and 5 % Dextrose Injection.

Remifentanil does not contain an antimicrobial preservative. Therfore 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 2-8ºC, 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 25ºC.
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 Remifentanil 1 mg with chlorobutyl plug and flip-off capsule.
3 ml vial (type-I colorless glass) of Remifentanil 2 mg with chlorobutyl plug and flip-off capsule.
- 6 ml vial (type-I colorless glass) of Remifentanil 5 mg with chlorobutyl plug and flip-off capsule.

Packs of 5 vials.

6.6. Special precautions for disposal

To prepare Remifentanil 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, discoluoration 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.

Remifentanil 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.

Remifentanil is comptabile 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

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

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

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

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of		
	25μg/ml 1mg/40ml	50μg/ml 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 Remifentanil 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 Remifentanil 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 Remifentanil 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 Remifentanil 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	5.40	6.00
0.5	3.60	4.80	6.00	7.20	8.40	9.60	10.80	12.00
0.75	5.40	7.20	9.00	10.80	12.60	14.40	16.20	18.00
1.0	7.20	9.60	12.00	14.40	16.80	19.20	21.60	24.00
1.25	9.00	12.00	15.00	18.00	21.00	24.00	27.00	30.00
1.5	10.80	14.40	18.00	21.60	25.20	28.80	32.40	36.00
1.75	12.60	16.80	21.00	25.20	29.40	33.60	37.80	42.00
2.0	14.40	19.20	24.00	28.80	33.60	38.40	43.20	48.00

7. LICENSES NUMBERS:

Remifentanil BioAvenir 1mg : 151-95-33782-00
Remifentanil BioAvenir 2mg : 151-96-33785-00
Remifentanil BioAvenir 5mg : 151-97-33786-00

8. MARKETING AUTHORIZATION HOLDER

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9. LICENSE HOLDER AND IMPORTER

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