AUSTRALIAN PRODUCT INFORMATION

REMIFENTANIL VIATRIS

(remifentanil (as hydrochloride)) powder for injection

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, REMIFENTANIL VIATRIS should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hazardous and harmful use

REMIFENTANIL VIATRIS poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of REMIFENTANIL VIATRIS. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking REMIFENTANIL VIATRIS.

1 NAME OF THE MEDICINE

Remifentanil (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each REMIFENTANIL VIATRIS powder for injection vial contains 1 mg, 2 mg or 5 mg of remifentanil (as hydrochloride) as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

REMIFENTANIL VIATRIS is a sterile, endotoxin free, non-pyrogenic, preservative-free, white to off-white lyophilised powder for intravenous injection or infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REMIFENTANIL VIATRIS is indicated

- as an opioid adjunct for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery in adults
- as an opioid adjunct for use during induction and/or maintenance of general anaesthesia during surgical but not cardiac procedures in children aged 1 to 12 years
- for continuation as an analgesic into the immediate post-operative period under the close supervision of medically qualified persons trained in the use of anaesthetic drugs, during transition to longer acting analgesia following adult cardiac surgery - when endotracheal intubation and controlled ventilation are anticipated
- for provision of analgesia and sedation in mechanically ventilated intensive care patients

4.2 DOSE AND METHOD OF ADMINISTRATION

REMIFENTANIL VIATRIS should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by medically qualified 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 intubation, and assisted ventilation.

Continuous infusions of REMIFENTANIL VIATRIS must be administered by a calibrated infusion device, where possible via a dedicated intravenous line, otherwise into a fast flowing IV line. The remifentanil infusion line should be connected at, or close to, the intravenous cannula and primed, to minimise the potential dead space (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use for additional information, including tables with examples of infusion rates by body weight to help titrate remifentanil to the patient's anaesthetic needs).

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Failure to clear the intravenous tubing to remove residual remifentanil has been associated with the appearance of respiratory depression, apnoea and muscle rigidity upon later administration of fluids or medications through the same IV tubing.

REMIFENTANIL VIATRIS is for intravenous use only and must not be administered by epidural or intrathecal injection (see Section 4.3 CONTRAINDICATIONS).

Administration by Manually-Controlled Infusion

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

Administration by Target-Controlled Infusion

REMIFENTANIL VIATRIS may also be given by target-controlled infusion (TCI) with an approved infusion device incorporating a validated pharmacokinetic model (the Minto pharmacokinetic model with covariates for age and lean body mass (LBM) is an example of a model available with current devices).

TCI can be used for induction and maintenance of ASA I and II adult patients in general and cardiac anaesthesia. There are insufficient data to make recommendations for delivery of REMIFENTANIL VIATRIS by TCI for ASA III and IV patients, spontaneous ventilation anaesthesia, use in ICU sedation, monitored conscious sedation or in children.

For TCI in adults the recommended dilution of REMIFENTANIL VIATRIS is 20 to 50 micrograms/mL.

General Anaesthesia

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

Dosage in Adults

Administration by Manually-Controlled Infusion

Table 1 summarises the starting infusion rates and dose range for various anaesthetic situations:

Table 1: Dosing Guidelines for Adults

INDICATION	**Remifentanil**	**Remifentanil Continuous Infusion**	
	Slow Bolus Injection (microgram/kg)	**Starting Rate (microgram/kg/min)**	**Range (microgram/kg/min)**
Induction of anaesthesia	1 (administer over 60 seconds)*	0.5 to 1	-
Maintenance of anaesthesia e.g. with any one of: • Nitrous oxide (66%) • Isoflurane (starting dose 0.5 MAC) • Propofol (starting dose 100 microgram/kg/min)	0.5 – 1	0.4 0.25 0.25	0.1 to 2 0.05 to 2 0.05 to 2

MAC = minimum alveolar concentration

* When given by bolus infusion AT INDUCTION, REMIFENTANIL VIATRIS should be administered over 60 seconds (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Muscle Rigidity).

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use for additional information, including tables to help titrate REMIFENTANIL VIATRIS to the patient's anaesthetic needs.

At the doses recommended above, REMIFENTANIL VIATRIS 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Concomitant Medication).

No data are available for dosage recommendations for simultaneous use of other hypnotics with REMIFENTANIL VIATRIS.

<u>Induction of Anaesthesia</u>

REMIFENTANIL VIATRIS should be administered with a hypnotic agent, such as propofol, thiopentone or isoflurane, for the induction of anaesthesia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Muscle Rigidity: Prevention and Management). REMIFENTANIL VIATRIS can be administered at an infusion rate of 0.5 to 1 microgram/kg/min with or without an initial bolus infusion of 1 microgram/kg over 60 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the infusion of REMIFENTANIL VIATRIS, then a bolus infusion is not necessary.

Maintenance of Anaesthesia in Ventilated Patients

After endotracheal intubation, the infusion rate of REMIFENTANIL VIATRIS 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 VIATRIS, 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 μ-opioid response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 to 5 minutes.

Analgesia

On cessation of infusion, remifentanil has a short-lasting analgesic effect. Post-operative pain management should be considered and, where appropriate, begun prior to the termination of remifentanil infusion.

Guidelines for Discontinuation

Upon discontinuation of remifentanil, the intravenous tubing should be cleared to prevent the inadvertent administration of remifentanil at a later point in time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Due to the 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 generally anticipated, alternative 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 follow-up care.

Concomitant Medication

Remifentanil decreases the dose of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Administration by Target-Controlled Infusion

Induction and Maintenance of Anaesthesia in Ventilated Patients

REMIFENTANIL VIATRIS TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 1). In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanil concentrations ranging from 3 to 8 ng/mL. REMIFENTANIL VIATRIS should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 ng/mL may be required.

As with manually controlled infusion, at the doses recommended above, REMIFENTANIL VIATRIS 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 (see Table 1).

There are insufficient data to make recommendations on the use of TCI for spontaneous ventilation anaesthesia.

Guidelines for Discontinuation/Continuation into the Immediate Post-operative Period

At the end of surgery when the TCI infusion is stopped, or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Anaesthesia: Dosage in Adults: Guidelines for discontinuation).

There are insufficient data to make recommendations on the use of TCI for the management of post-operative analgesia.

Dosage in Paediatric Patients (1-12 years of age)

Administration by Manually-Controlled Infusion

Induction of Anaesthesia

There are insufficient data to make a dosage recommendation.

Maintenance of Anaesthesia

Table 2: Dosing Guidelines for Maintenance of Anaesthesia in Paediatric Patients (1 – 12 years of age)

Concomitant Anaesthetic Agent*	Remifentanil Bolus Injection Optional (microgram/kg)	Remifentanil Continuous Infusion (microgram/kg/min)	
		Starting Rate	Typical Maintenance Rates
Halothane (starting dose 0.3 MAC)	1	0.25	0.05 to 1.3
Sevoflurane (starting dose 0.3 MAC)	1	0.25	0.05 to 0.9
Isoflurane (starting dose 0.5 MAC)	1	0.25	0.06 to 0.9

*co-administered with nitrous oxide/oxygen in a ratio of 2:1

When given by bolus injection REMIFENTANIL VIATRIS should be administered over not less than 30 seconds. Surgery should not commence until at least 5 minutes after the start of the remifentanil infusion, if a simultaneous bolus dose has not been given. Paediatric patients should be monitored, and the dose titrated to the depth of analgesia appropriate for the surgical procedure.

Concomitant Medication

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore isoflurane, halothane and sevoflurane should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Anaesthesia: Dosage in Adults: Concomitant Medication).

Guidelines for Discontinuation

Following discontinuation of the infusion, the offset of analgesic effect of remifentanil is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be anticipated and implemented (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Anaesthesia: Dosage in Adults: Guidelines for Discontinuation).

Administration by Target-Controlled Infusion

Remifentanil TCI has not been studied in paediatric patients.

Paediatric Patients Aged Less Than 1 Year

The pharmacokinetic profile of remifentanil in paediatric patients aged more than 2 months is comparable to that seen in adults after correction for body weight differences. However, there are insufficient pharmacokinetic and clinical data to make dosage recommendations for patients aged less than 1 year.

Cardiac Anaesthesia

Dosage in Adults

Administration by Manually-Controlled Infusion

Table 3: Dosing Guidelines for Cardiac Anaesthesia

Indication	Remifentanil Bolus Injection (microgram/kg)	Remifentanil Continuous Infusion (microgram/kg/min)	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	-
Maintenance of anaesthesia			
• Isoflurane (starting dose 0.4 MAC)	0.5 to 1	1	0.003 to 4
• Propofol (starting dose 50 microgram/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

Induction Period of Anaesthesia

After administration of hypnotic to achieve loss of consciousness, REMIFENTANIL VIATRIS should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus injections of REMIFENTANIL VIATRIS during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 6 minutes after the start of infusion in order to minimise the response to intubation.

Maintenance Period of Anaesthesia

After endotracheal intubation the infusion rate of REMIFENTANIL VIATRIS should be titrated according to patient need. Supplemental bolus doses may also be given as required. High risk cardiac patients, such as those with poor ventricular function, should be administered a maximum bolus dose of 0.5 microgram/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see Section 5.2 PHARMACOKINETIC PROPERTIES – Additional Pharmacokinetic Information: Cardiac Anaesthesia).

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 DOSE AND METHOD OF ADMINISTRATION - General Anaesthesia: Dosage in Adults: Concomitant Medication).

Continuation of Post-operative Analgesia Prior to Extubation

It is recommended that the infusion of REMIFENTANIL VIATRIS 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 VIATRIS rate adjusted to meet the individual patient's requirements.

Guidelines for Discontinuation

REMIFENTANIL VIATRIS should only be continued as an analgesic in the immediate post-operative period, and subsequently discontinued during transition to longer acting analgesia, in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by medically qualified 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 intubation, and assisted ventilation.

Prior to discontinuation of REMIFENTANIL VIATRIS, patients must be given alternative analgesic and sedative agents at a sufficient time in advance. The choice and dose of agent(s) should be appropriate for the patient's level of post-operative care (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Anaesthesia: Dosage in Adults: Guidelines for Discontinuation).

It is recommended that the REMIFENTANIL VIATRIS infusion is discontinued by reducing the infusion rate by 25% decrements in at least 10 minute intervals until the infusion is discontinued. During weaning from the ventilator, the REMIFENTANIL VIATRIS 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.

Administration by Target-Controlled Infusion

There are insufficient data to make recommendations for delivery of REMIFENTANIL VIATRIS by TCI for ASA III and IV patients undergoing cardiac surgery.

There are insufficient data to make recommendations on the use of TCI for the management of post-operative analgesia.

Induction and Maintenance of Anaesthesia

Remifentanil TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 3). In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 ng/mL have been used in clinical studies. At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia (see Table 3).

Guidelines for Discontinuation/Continuation into the Immediate Post-operative Period

At the end of surgery when the TCI infusion is stopped, or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Cardiac Anaesthesia: Dosage in Adults: Administration by Manually-Controlled Infusion-Guidelines for discontinuation).

Dosage in Paediatric patients

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

Special Patient Populations

Dosage in Elderly Patients (over 65 years of age)

General Anaesthesia

The initial starting dose of REMIFENTANIL VIATRIS administered to patients over 65 should be half the recommended adult dose and then 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 DOSE AND METHOD OF ADMINISTRATION - Cardiac Anaesthesia: Dosage in Adults-Table 3: Dosing Guidelines for Cardiac Anaesthesia).

Administration by Manually-Controlled Infusion

Intensive Care

No initial dose reduction is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Special Patient Populations: Use in Intensive Care).

Administration by Target-Controlled Infusion

General Anaesthesia

Because of the increased sensitivity of elderly patients to remifentanil, when administering REMIFENTANIL VIATRIS by TCI in this population the initial target concentration should be 1.5 to 4 ng/mL with subsequent titration to response.

Dosage in Obese Patients

Administration by Manually-Controlled Infusion

For manually controlled infusion, it is recommended that for obese patients the dosage of REMIFENTANIL VIATRIS 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.

Administration by Target-Controlled infusion

With the calculation of lean body mass (LBM) used in Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m^2 and in male patients with BMI greater than 40 kg/m^2. To avoid under dosing in these patients, REMIFENTANIL VIATRIS TCI should be titrated carefully to individual response.

Dosage in Patients with Renal Impairment

No dosage adjustment, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of remifentanil is unchanged in this patient population.

Dosage in Patients with Hepatic Impairment

No adjustment of the initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of remifentanil is unchanged in this patient population. However, 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 VIATRIS titrated to individual patient needs.

Neurosurgery

There is limited clinical experience with patients undergoing neurosurgery.

ASA III/IV patients

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 VIATRIS in this population.

Manually Controlled Infusion: Initial dosage reduction and subsequent titration to effect is therefore recommended.

Target-Controlled Infusion: TCI is not recommended for ASA III or IV patients.

Cardiac Anaesthesia

No initial dose reduction is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Cardiac Anaesthesia Table 3: Dosing Guidelines for Cardiac Anaesthesia).

Intensive Care

No initial dose reduction is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Special Patient Populations: Use in Intensive Care).

Use in Intensive Care

Administration by Manually Controlled Infusion

REMIFENTANIL VIATRIS can be initially used alone for the provision of analgesia and sedation in mechanically ventilated intensive care patients.

It is recommended that REMIFENTANIL VIATRIS is initiated at an infusion rate of 0.1 microgram/kg/min to 0.15 microgram/kg/min.

The infusion rate should be titrated in increments of 0.025 microgram/kg/min 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 VIATRIS infusion rate adjusted accordingly. If an infusion rate of 0.2 microgram/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 remifentanil infusion rate in increments of 0.025 microgram/kg/min may be made if additional analgesia is required.

Remifentanil has been studied in intensive care patients in well controlled clinical trials for up to three days (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials: Intensive Care Unit).

Table 4 summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients.

Table 4: Dosing Guidelines for Use OF Remifentanil Within the Intensive Care Setting

Continuous Infusion Microgram/kg/min	
Starting Rate	**Maintenance Range ***
0.1 to 0.15	0. 006 to 0.74

***** Range of doses used in clinical trials to maintain adequate analgesia and sedation.

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

The use of REMIFENTANIL VIATRIS will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given in Table 5.

Table 5: 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 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 0.1mcg/kg/min should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25%-50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25microgram/kg/min, maximum 0.75microgram/kg/min, has been administered for provision of additional anaesthesia 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. 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. The range of options for analgesia includes long acting oral, intravenous, or regional analgesics controlled by the nurse of the patient. These techniques should always be titrated to individual patient need as the infusion of remifentanil is reduced (see below). It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to 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 down in stages to 0.1mcg/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-minute 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.

Paediatric Intensive Care Patients

There are no data available on use in paediatric patients.

Renally-impaired Intensive Care Patients

No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy.

Recovery following discontinuation of a remifentanil infusion may be slightly prolonged in moderate to severe renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES – Additional Pharmacokinetic Information: Pharmacokinetics in Patients with Renal Impairment).

Administration by Target-Controlled Infusion

Remifentanil TCI has not been studied in intensive care patients.

Instructions for Use

Reconstitution and Dilution

To reconstitute the powder, add 1 mL of diluent (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use: Physical Compatibilities for recommended diluents) per mg of remifentanil. Shake well to dissolve. When reconstituted as directed, the solution contains approximately 1 mg of remifentanil activity per 1 mL.

REMIFENTANIL VIATRIS should be diluted to a final concentration of 20, 25, 50, or 250 microgram/mL prior to administration (see Table 6).

50 microgram/mL is the recommended dilution for adults and 20-25 microgram/mL for paediatric patients aged 1 year and over. The dilution is dependent upon the technical capability of the infusion device and the expected requirements of the patient. REMIFENTANIL VIATRIS should not be administered without dilution.

Table 6: Reconstitution and Dilution of Remifentanil

Final Concentration	Amount of Remifentanil in each vial	Final Volume after Reconstitution and Dilution
20 microgram/mL	1 mg	50 mL
	2 mg	100 mL
	5 mg	250 mL
25 microgram/mL	1 mg	40 mL
	2 mg	80 mL
	5 mg	200 mL
50 microgram/mL	1 mg	20 mL
	2 mg	40 mL
	5 mg	100 mL
250 microgram/mL	5 mg	20 mL

Physical Compatibilities

REMIFENTANIL VIATRIS is chemically and physically stable and should be used within 24 hours of preparation and storage at 2 to 8°C, after reconstitution and further dilution to concentrations of 20 to 250 microgram/mL with one of the following recommended intravenous fluids:

- Sterile Water for Injection
- 5% Glucose Injection
- 5% Glucose and 0.9% Sodium Chloride Injection
- 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Injection

REMIFENTANIL VIATRIS contains no antimicrobial preservative and care must be taken to assure the sterility of prepared solutions. Reconstituted product should be used promptly, and any unused material discarded. If storage is necessary, hold at 2 to 8°C for not more than 24 hours to reduce microbiological hazard (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use: Physical Incompatibilities).

Remifentanil has been shown to be compatible with the following intravenous fluids when administered into a running intravenous line of:

- Lactated Ringer's Injection
- Lactated Ringer's and 5% Glucose Injection

Remifentanil has been shown to be compatible with propofol when administered into a running intravenous line.

Physical Incompatibilities

Continuous infusions of REMIFENTANIL VIATRIS must be administered by a calibrated infusion device, where possible via a dedicated intravenous line, otherwise into a fast flowing IV line.

REMIFENTANIL VIATRIS should only be reconstituted and diluted with those infusion solutions recommended (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use: Physical Compatibilities).

REMIFENTANIL VIATRIS should not be reconstituted, diluted, or mixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Glucose Injection.

REMIFENTANIL VIATRIS should not be mixed with propofol in the same infusion bag prior to administration.

Administration of REMIFENTANIL VIATRIS into the same intravenous line with blood/serum/plasma is not recommended. Non-specific esterase in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

REMIFENTANIL VIATRIS should not be mixed with other therapeutic agents prior to administration.

Administration by Manually-Controlled Infusion

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

The following tables give guidelines for infusion rates of remifentanil by manually-controlled infusion.

Table 7: Remifentanil for Injection Infusion Rates (mL/kg/h)

Drug Delivery Rate (microgram/kg/min)	Infusion Delivery Rate (mL/kg/h)			
	20 microgram/mL 1 mg/50 mL	25 microgram/mL 1 mg/40 mL	50 microgram/mL 1 mg/20 mL	250 microgram/mL 10 mg/40 mL
0.0125	0.038	0.03	0.015	Not recommended
0.025	0.075	0.06	0.03	Not recommended
0.05	0.15	0.12	0.06	0.012
0.075	0.23	0.18	0.09	0.018
0.1	0.3	0.24	0.12	0.024
0.15	0.45	0.36	0.18	0.036
0.2	0.6	0.48	0.24	0.048
0.25	0.75	0.6	0.3	0.06
0.5	1.5	1.2	0.6	0.12

0.75	2.25	1.8	0.9	0.18
1.0	3.0	2.4	1.2	0.24
1.25	3.75	3.0	1.5	0.3
1.5	4.5	3.6	1.8	0.36
1.75	5.25	4.2	2.1	0.42
2.0	6.0	4.8	2.4	0.48

Table 8: Remifentanil for Injection Infusion Rates (mL/h) for a 20 microgram/mL Solution

Infusion Rate (microgram/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 9: Remifentanil for Injection Infusion Rates (mL/h) for a 25 microgram/mL Solution

Infusion Rate (microgram/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
.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
.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 10: Remifentanil for Injection Infusion Rates (mL/h) for a 50 microgram/mL Solution

Infusion Rate (microgram/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

Infusion Rate (microgram/kg/min)	Patient Weight (kg)							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
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 11: Remifentanil for Injection Infusion Rates (mL/h) for a 250 microgram/mL Solution

Infusion Rate (microgram/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

Administration by Target-Controlled Infusion

For TCI the recommended dilution of REMIFENTANIL VIATRIS is 20 to 50 micrograms/mL.

The following table gives guidelines for blood concentrations achieved at steady state with MCI in a 70 kg, 170 cm, 40 year-old, male patient (using Minto PK model).

Table 12: Blood Concentrations Achieved at Steady State with MCI in a 70 kg, 170 cm, 40 Year-Old, Male Patient (using Minto PK model)

Remifentanil Infusion Rate (microgram/kg/min)	Remifentanil Blood Concentration (ng/mL)
0.05	1.3
0.10	2.6
0.25	6.3

Remifentanil Infusion Rate (microgram/kg/min)	Remifentanil Blood Concentration (ng/mL)
0.40	10.4
0.50	12.6
1.0	25.2
2.0	50.5

Discontinuation

Upon discontinuation of REMIFENTANIL VIATRIS sufficient drug may remain in intravenous lines or in the dead space of cannulae to cause opioid-related effects (e.g. respiratory depression) if the line is flushed. Therefore, appropriate measures should be taken to avoid such inadvertent administration of REMIFENTANIL VIATRIS (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

REMIFENTANIL VIATRIS is not suitable as the sole agent for induction of general anaesthesia.

REMIFENTANIL VIATRIS is not recommended for use in spontaneous ventilation anaesthesia or as an analgesic in the immediate post-operative period due to inadequate safety data in such uses, except in ventilated cardiac surgery patients (see Section 4.1 THERAPEUTIC INDICATIONS and Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Cardiac Anaesthesia).

As glycine is present in the formulation, REMIFENTANIL VIATRIS is contraindicated for epidural and intrathecal use.

REMIFENTANIL VIATRIS is contraindicated for use in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

REMIFENTANIL VIATRIS is contraindicated for use in chronic (long-term) non-cancer pain.

REMIFENTANIL VIATRIS is contraindicated in patients with known hypersensitivity to any component of the preparation and to other fentanyl analogues.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 (see Section 4.3 CONTRAINDICATIONS).

Hazardous and harmful use

REMIFENTANIL VIATRIS contains the opioid remifentanil hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed REMIFENTANIL VIATRIS at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed REMIFENTANIL VIATRIS.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share REMIFENTANIL VIATRIS with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of remifentanil but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with severe hepatic impairment and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see Section 4.3 CONTRAINDICATIONS).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

<u>The Use of Remifentanil may be Associated with Apnoea and Respiratory Depression</u>

Remifentanil should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by medically qualified 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 intubation and assisted ventilation.

<u>Respiratory Depression - Management</u>

The use of remifentanil may be associated with apnoea and respiratory depression. Therefore, remifentanil should only be used where facilities for monitoring and treating respiratory depression are available. The occurrence of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50% or a temporary discontinuation of the infusion. Remifentanil has not been shown to cause recurrent respiratory depression even after prolonged administration. However, respiratory depression may occur in some patients up to 30 minutes after cessation of the remifentanil infusion due to residual effects of concomitant anaesthetics, and therefore it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Inadvertent Administration).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal

insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with REMIFENTANIL VIATRIS should be considered.

Endocrine effects

Opioids, such as REMIFENTANIL VIATRIS, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Hormonal disturbances that have been observed include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Neonatal withdrawal syndrome

Chronic use of remifentanil by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see Section 4.6 - USE IN PREGNANCY).

Gastrointestinal toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in hypotension, sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of REMIFENTANIL VIATRIS with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe remifentanil concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking REMIFENTANIL VIATRIS.

Risks of use in patients with biliary tract disease

Remifentanil hydrochloride may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing REMIFENTANIL VIATRIS in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Accidental ingestion/exposure

Accidental ingestion or exposure of REMIFENTANIL VIATRIS, especially by children, can result in a fatal overdose of remifentanil hydrochloride. Patients and their caregivers should be given information on safe storage and disposal of unused REMIFENTANIL VIATRIS (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Rapid Offset of Action

Within 5 to 10 minutes after the discontinuation of remifentanil no residual opioid activity will be present.

For those patients undergoing surgical procedures where post-operative pain is generally anticipated alternative analgesics should be administered prior to the 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 follow-up care.

Discontinuation of Treatment

Symptoms including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of remifentanil. Where reported, re-introduction and tapering of the infusion has been beneficial.

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. Remifentanil should be administered, where possible via a dedicated IV line which is removed when remifentanil is discontinued, otherwise into a fast flowing IV line at or close to the venous cannula and primed, in order to avoid administration of drug into the single dead space.

Muscle Rigidity - Prevention and Management

At the recommended doses, remifentanil can cause muscle rigidity. Profound chest wall rigidity and inability to ventilate the patient has occurred during induction and following inadvertent boluses after intravenous line flushing. The incidence of muscle rigidity is related to the dose and rate of administration. Therefore, boluses should be administered slowly, over 60 seconds.

Muscle rigidity induced by remifentanil must be treated in the context of the patient's clinical condition with appropriate supporting measures. 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 and may require intubation for ventilation.

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. In the case of life-threatening muscle rigidity, a rapid onset neuromuscular blocker or an opioid antagonist may be administered.

Cardiovascular Effects

Remifentanil causes dose-dependent hypotension and bradycardia. These effects may be attenuated by the pre-administration of an appropriate anticholinergic agent such as glycopyrronium bromide or atropine. Hypotension and bradycardia may be managed by reducing the rate of infusion of remifentanil or the dose of concurrent anaesthetics, and by using intravenous fluids, vasopressor or anticholinergic agents as appropriate.

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

Awareness

Intraoperative awareness has been reported when remifentanil has been administered with propofol infusion rates less than 75 microgram/kg/min.

Use in Hepatic Impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Special Patient Populations: Dosage in Patients with Hepatic Impairment.

Use in Renal Impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Special Patient Populations: Dosage in Patients with Renal Impairment.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Special Patient Populations: Dosage in Elderly Patients (over 65 years of age).

Paediatric Use

There are insufficient data available on use in paediatric patients under 1 year of age.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Remifentanil is not metabolised by plasma cholinesterase, therefore interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, remifentanil decreases the dose of inhaled and intravenous anaesthetics and benzodiazepines required for anaesthesia (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents. See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants including alcohol.

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.

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

Monoamine oxidase inhibitor (MAOI) interactions with opioids may manifest as serotonin syndrome.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Daily administration of remifentanil to male rats was associated with pathological changes in the epididymides at exposures to remifentanil and its major metabolite GR90291 of < 1 and > 200-fold, respectively, the anticipated clinical exposure, and pathological changes in the testes and reduced fertility and pregnancies at exposures to remifentanil and GR90291 of 1-2 and > 600-fold, respectively, the anticipated clinical exposure.

Use in Pregnancy

Pregnancy category: C

Although placental transfer of remifentanil and its major metabolite GR90291 was found in rats, rabbits and monkeys, there was no evidence of teratogenicity in rats at exposures to remifentanil and its major metabolite of 6 and > 200-fold, respectively, the anticipated clinical exposure. In rabbits, teratogenicity was observed only at remifentanil doses greater than those producing maternotoxicity and fetotoxicity, with remifentanil exposures of about 200-fold anticipated human remifentanil exposure. However, there are no adequate and well controlled studies in pregnant women. The use of remifentanil in pregnant women is not recommended. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of remifentanil during pregnancy.

Use in Lactation

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, caution should be exercised when remifentanil is administered to mothers who are breastfeeding.

Use in Obstetrics

The safety profile of remifentanil during labour or delivery has not been demonstrated. Remifentanil should not be used during labour and caesarean Sections because it is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Following treatment using anaesthetic agents, patients should be advised not to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most common adverse events associated with remifentanil are direct extensions of μ-opioid agonist pharmacology, such as respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. These are dose dependent events and hence dissipate within minutes of discontinuing or decreasing the infusion rate of remifentanil. Hypotension may be relatively more common in the elderly (> 65 years).

Approximately 3,800 patients have been exposed to remifentanil in controlled clinical trials.

The frequencies of adverse events during general anaesthesia with the recommended doses of remifentanil are given in Table 13. Each patient was counted once for each type of adverse event.

Table 13: Adverse Events Reported in ≥ 1% of Patients in General Anaesthesia Studies at the Recommended Doses of Remifentanil*

Adverse Event	Induction/Maintenance		After Discontinuation	
	Remifentanil	Alfentanil/Fentanyl	Remifentanil	Alfentanil/Fentanyl
	(n = 921)	(n = 466)	(n = 929)	(n = 466)
GASTROINTESTINAL				
Nausea	< 1%	0	36%	43%
Vomiting	< 1%	< 1%	16%	20%
CARDIOVASCULAR				
Hypotension	19%	6%	2%	2%
Bradycardia	7%	5%	1%	1%
Hypertension	1%	2%	1%	2%
Tachycardia	< 1%	2%	1%	2%
RESPIRATORY				
Respiratory Depression	< 1%	0	2%	4%
Apnoea	0	< 1%	< 1%	< 1%
Hypoxia	0	0	1%	2%
MUSCULOSKELETAL				
Muscle Rigidity	11%#	8%	< 1%	< 1%
Shivering	< 1%	0	5%	2%
NEUROLOGICAL				
Fever	< 1%	0	5%	2%
Dizziness	0	0	3%	2%
Visual disturbance	0	0	3%	3%
Headache	0	0	2%	2%
Post-operative Pain	0	0	< 1%	1%
Agitation	< 1%	0	< 1%	< 1%
DERMATOLOGICAL				
Pruritus	< 1%	0	2%	2%

The doses of comparator opioids used in these studies were as follows:

- Alfentanil: 20 - 50 microgram/kg bolus + 0.5 - 2 microgram/kg/min infusion.
- Fentanyl: 3 microgram/kg bolus + 1.5 - 3 microgram/kg bolus doses as required.

* See Table 1 for recommended doses of remifentanil. Not all doses of remifentanil were equipotent to the comparator opioid. Administration of remifentanil in excess of the recommended dose (i.e., doses > 1 and up to 20 mg/kg) resulted in a higher incidence of some adverse events: muscle rigidity (37%), bradycardia (12%), hypertension (4%), and tachycardia (4%).

Included in the muscle rigidity incidence is chest wall rigidity (5%). The overall muscle rigidity incidence is < 1% when remifentanil is administered concurrently or after a hypnotic induction agent.

Cardiac Anaesthesia

The side-effect profile of remifentanil was consistent with the known pharmacology of μ-opioid agonists. Hypotension observed in maintenance regimens (4% vs. 1%); and hypertension (2% vs. 0%), shivering (4% vs. 2%) and aches (2% vs. 0%) observed post-operatively; occurred at a greater frequency with remifentanil compared to "fast-track" comparator opioid (fentanyl and sufentanil) regimens. Although there was a higher frequency of the above adverse events, the incidence of adverse cardiac outcomes in each of the randomised, double-blind trials was similar for remifentanil and comparator opioid.

Paediatric Anaesthesia

Remifentanil was well tolerated and the incidence of adverse events at the recommended doses was similar to that reported for adults.

Intensive Care Unit

The overall incidence of drug-related adverse events across treatment groups was: remifentanil 22% vs. fentanyl 17% vs. morphine 16%. The incidence of hypotension was comparable between groups (remifentanil 9% vs. fentanyl 9% vs. morphine 7%); the majority of hypotensive reports being drug-related (remifentanil 6% vs. fentanyl 6% vs. morphine 6%). Episodes of hypotension (defined as a mean arterial pressure, 50 mmHg) were more frequent with remifentanil (11% - 17% compared with morphine 2% and fentanyl 10%) however this was not associated with an increase in adverse event reporting (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Cardiovascular effects). In the remifentanil group the majority of drug related episodes of hypotension were mild or moderate in severity and in the majority of cases, the average duration was less than 20 minutes.

Pruritus was one of the most commonly reported drug-related adverse events in the remifentanil group (2% incidence).

Other Adverse Events

Less commonly reported adverse clinical events (incidence < 1%) from all controlled studies are presented below:

Digestive: constipation, abdominal discomfort, xerostomia, gastro-oesophageal reflux, dysphagia, diarrhoea, heartburn, ileus.

Cardiovascular: various atrial and ventricular arrhythmias, heart block, ECG change consistent with myocardial ischaemia, elevated CPK-MB level, syncope.

Musculoskeletal: muscle stiffness, musculoskeletal chest pain, post-operative aches.

Respiratory: cough, dyspnoea, bronchospasm, laryngospasm, rhonchi, stridor, nasal congestion, pharyngitis, pleural effusion, hiccups, pulmonary oedema, rales, bronchitis, rhinorrhoea.

Nervous: anxiety, involuntary movement, prolonged emergence from anaesthesia, confusion, awareness under anaesthesia without pain, rapid awakening from anaesthesia, tremors, disorientation, dysphoria, nightmares, hallucinations, paraesthesia, nystagmus, twitch, sleep disorder, seizure, amnesia.

Body as a whole: decreased body temperature, anaphylactic reaction, delayed recovery from neuromuscular block.

Skin: rash, urticaria.

Urogenital: urine retention, oliguria, dysuria, urine incontinence.

Infusion site reactions: erythema, pruritus, rash.

Metabolic and nutrition: abnormal liver function, hyperglycaemia, electrolyte disorders, increased CPK level.

Haematologic and lymphatic: anaemia, lymphopenia, leukocytosis, thrombocytopenia.

Observed during clinical practice: in addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of remifentanil in conjunction with one or more anaesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to remifentanil.

Non-site specific: very rarely, allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents.

Cardiovascular: rare cases of asystole/cardiac arrest, usually preceded by bradycardia, have been reported in patients receiving remifentanil in conjunction with other anaesthetic agents.

Post-marketing experience

Respiratory disorders with a frequency not known: Central sleep apnoea syndrome

Gastrointestinal disorders with a frequency not known: Pancreatitis

Hepatobiliary disorders with a frequency not known: Spasm of sphincter of Oddi

Endocrine disorders with a frequency not known: Adrenal insufficiency and Androgen deficiency

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute overdose with remifentanil hydrochloride can be manifested by respiratory depression, toxic leukoencephalopathy, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary oedema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death.

Overdosage is manifested by an extension of the pharmacologically predictable actions of REMIFENTANIL VIATRIS.

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

Intravenous administration of naloxone may be given as a specific antidote to manage severe respiratory depression and muscle rigidity.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Remifentanil is a potent, selective, 4-anilidopiperidine μ-opioid agonist with pharmacological action typical of this class of compound. It is distinguished from other 4-anilidopiperidines (fentanyl analogues) by its rapid onset and very short duration of action. The μ-opioid activity of remifentanil is antagonised by naloxone. Remifentanil in humans has a rapid blood-brain equilibration half-time of 1 ± 1 minutes (mean ± SD) and a rapid onset of action. The pharmacodynamic effects of remifentanil closely follow the measured blood concentrations, allowing direct correlation between dose, blood levels, and response. Blood concentration decreases 50% in 3 to 6 minutes after a 1-minute infusion or after prolonged continuous infusion due to rapid distribution and elimination processes and is independent of duration of drug administration. Recovery from the effects of remifentanil occurs rapidly (within 5 to 10 minutes). New steady-state concentrations occur within 5 to 10 minutes after changes in infusion rate. When used as a component of an anaesthetic technique, remifentanil can be rapidly titrated to the desired depth of anaesthesia/analgesia (e.g., as required by varying levels of intraoperative stress) by changing the continuous infusion rate or by administering an IV bolus injection. Remifentanil is a potent opioid, therefore careful adherence to information in Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE is essential to avoid unacceptable adverse events.

Haemodynamics

In premedicated patients undergoing anaesthesia, 1-minute infusions of <2 microgram/kg of remifentanil caused dose-dependent hypotension and bradycardia. While additional doses >2 microgram/kg (up to 30 microgram/kg) do not produce any further decreases in heart rate or blood pressure, the duration of the haemodynamic change is increased in proportion to the blood concentrations achieved. Peak haemodynamic effects occur within 3 to 5 minutes of a single dose of remifentanil or an infusion rate increase. Glycopyrronium bromide, atropine, and vagolytic neuromuscular blocking agents attenuate the haemodynamic effects associated with remifentanil. When appropriate, bradycardia and hypotension can be reversed by reduction of the rate of infusion of remifentanil, or the dose of concurrent anaesthetics, or by the administration of fluids or vasopressors.

Respiration

Remifentanil depresses respiration in a dose-related fashion. Unlike other fentanyl analogues, the duration of action of remifentanil at a given dose does not increase with increasing duration of administration, due to lack of drug accumulation. When remifentanil and alfentanil were dosed to equal levels of respiratory depression, recovery of respiratory drive after 3- hour infusions was more rapid and less variable with remifentanil (see Figure 1).

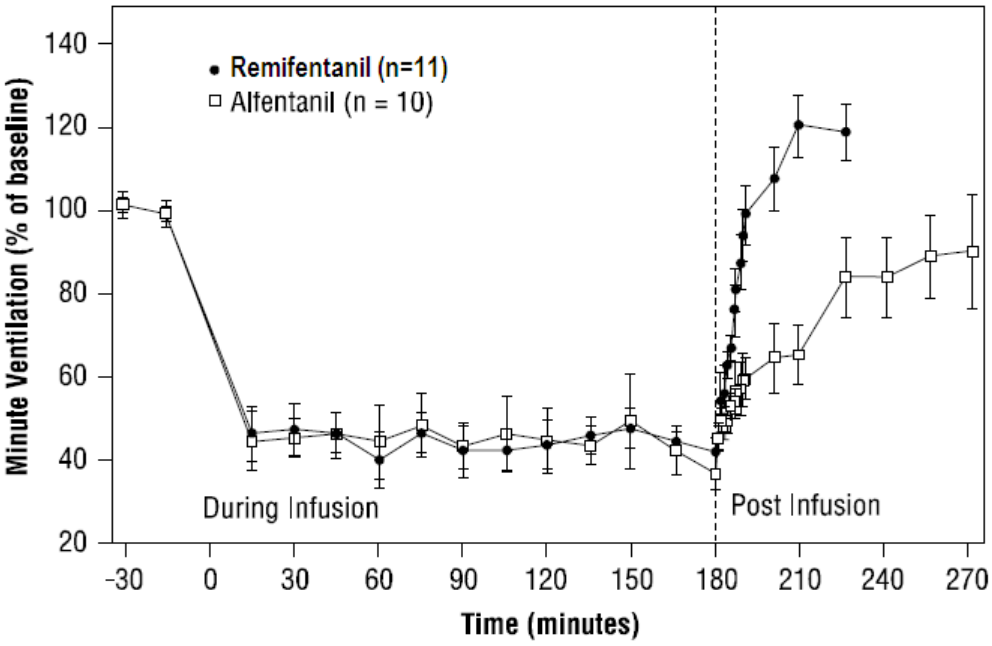


Figure 1: Recovery of Respiratory Drive after Equipotent* Doses of Remifentanil and Alfentanil using CO_2-Stimulated Minute Ventilation in Volunteers (± 1.5 SEM)

The infusion rates used in this study were 0.025 – 0.062 mg/kg/min for remifentanil and 0.19 – 0.48 microgram/kg/min for alfentanil.

*Equipotent refers to level of respiratory depression

Spontaneous respiration occurs at blood concentrations of 4 to 5 ng/mL in the absence of other anaesthetic agents, for example, after discontinuation of a 0.25 microgram/kg/min infusion of remifentanil, these blood concentrations would be reached in 2 to 4 minutes. In patients undergoing general anaesthesia, the rate of respiratory recovery depends upon the concurrent anaesthetic; it is fastest after N_2O, slower with propofol, and slowest after isoflurane.

Muscle Rigidity

Skeletal muscle rigidity can be caused by remifentanil and is related to the dose and speed of administration. Remifentanil may cause chest wall rigidity (inability to ventilate) after single doses of > 1 microgram/kg administered over 30 to 60 seconds or infusion rates >0.1 microgram/kg/min. Administration of doses < 1 microgram/kg may cause chest wall rigidity when given concurrently with a continuous infusion of remifentanil.

Histamine Release

Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after administration of remifentanil in doses up to 30 microgram/kg over 60 seconds.

Clinical Trials

Clinical trials have demonstrated that remifentanil is unsuitable as a sole agent for induction. For induction, remifentanil should only be used as an opioid adjunct where intubation and mechanical ventilation are intended. Remifentanil is not recommended for use in postoperative analgesia, except for ventilated cardiac surgery patients in an environment where the patient is under the close supervision of medically qualified persons trained in the use of anaesthetic drugs (see Section 4.1 THERAPEUTIC INDICATIONS and Section 4.3 CONTRAINDICATIONS).

Remifentanil was evaluated in 3,562 patients undergoing general anaesthesia (n = 2,923) and monitored anaesthesia care (n = 639). These patients were evaluated in the following settings: inpatient (n = 2,213) which included cardiovascular (n = 675) and neurosurgical (n = 61), and outpatient (n = 1,349). Three hundred

seventy-seven (377) elderly patients (age range 66 to 90 years) and 440 paediatric patients received remifentanil. Of the general anaesthesia patients, 1,132 also received remifentanil as an IV analgesic agent during the immediate postoperative period.

Induction and Maintenance of General Anaesthesia - Inpatient/Outpatient

The efficacy of remifentanil was investigated in 1562 patients in 15 randomised, controlled trials as the analgesic component for the induction and maintenance of general anaesthesia. Eight of these studies compared remifentanil to alfentanil, and two studies compared remifentanil to fentanyl. In these studies, doses of remifentanil up to the ED90 were compared to recommended doses (approximately ED50) of alfentanil or fentanyl.

Induction of Anaesthesia

Remifentanil was administered with isoflurane, propofol, or thiopentone for the induction of anaesthesia (n = 1,562). The majority of patients (80%) received propofol as the concurrent agent. Remifentanil reduced the propofol and thiopentone requirements for loss of consciousness. Compared to alfentanil and fentanyl, a higher relative dose of remifentanil resulted in fewer responses to intubation (see Table 14). Overall, hypotension occurred in 5% of patients receiving remifentanil compared to 2% of patients receiving the other opioids. Remifentanil has been used as a primary agent for the induction of anaesthesia; however, it should not be used as a sole agent because loss of consciousness cannot be assured and because of a high incidence of apnoea, muscle rigidity, and tachycardia. The administration of an induction dose of propofol or thiopentone or a paralysing dose of a muscle relaxant prior to or concurrently with remifentanil during the induction of anaesthesia markedly decreased the incidence of muscle rigidity from 20% to < 1%.

Table 14: Response to Intubation (Propofol/Opioid Induction*)

Opioid Treatment Group/(No. of patients)	Initial Dose (microgram/kg)	Pre-Intubation Infusion Rate (microgram/kg/min)	No. (%) Muscle Rigidity	No. (%) Hypotension During Induction	No. (%) Response to Intubation
Study 1					
Remifentanil (35)	1	0.1	1 (3%)	0	27 (77%)
Remifentanil (35)	1	0.4	3 (9%)	0	11 (31%)†
Alfentanil (35)	20	1.0	2 (6%)	0	26 (74%)
Study 2					
Remifentanil (116)	1	0.5	9 (8%)	5 (4%)	17 (15%)†
Alfentanil	25	1.0	6 (5%)	5 (4%)	33 (28%)
Study 3					
Remifentanil (134)	1	0.5	2 (1%)	4 (3%)	25 (19%)
Alfentanil (66)	20	2.0	0	0	19 (29%)
Study 4					
Remifentanil (98)	1	0.2	11 (11%)†	2 (2%)	35 (36%)
Remifentanil (91)	2‡	0.4	11 (12%)†	2 (2%)	12 (13%)†

Opioid Treatment Group/(No. of patients)	Initial Dose (microgram/kg)	Pre-Intubation Infusion Rate (microgram/kg/min)	No. (%) Muscle Rigidity	No. (%) Hypotension During Induction	No. (%) Response to Intubation
Fentanyl (97)	3	N/A	1 (1%)	1 (1%)	29 (30%)

* Propofol was titrated to loss of consciousness
† Differences were statistically significant ($p < 0.02$)
‡ Initial doses greater than 1 microgram/kg are not recommended

Use During Maintenance of Anaesthesia

Remifentanil was investigated in 929 patients in seven well-controlled general surgery studies in conjunction with nitrous oxide, isoflurane, or propofol in both inpatient and outpatient settings. These studies demonstrated that remifentanil could be dosed to high levels of opioid effect and rapidly titrated to optimise analgesia intraoperatively without delaying or prolonging recovery. Remifentanil was inadequate as a sole agent for maintenance of anaesthesia. Compared to alfentanil and fentanyl, these higher relative doses (ED90) of remifentanil resulted in fewer responses to intraoperative stimuli (see Table 15) and a higher frequency of hypotension (16% compared to 5% for the other opioids). Remifentanil was infused to the end of surgery, while alfentanil was discontinued 5 to 30 minutes before the end of surgery as recommended. The mean final infusion rates of Remifentanil were between 0.25 and 0.48 microgram/kg/min.

Table 15: Intraoperative Responses*

Opioid Treatment Group/(No. of patients)	Concurrent Anaesthetic	Post-Intubation Infusion Rate (microgram/kg/min)	No. (%) With Intraoperative Hypotension	No. (%) With Response to Skin Incision	No. (%) With Signs of Light Anaesthesia	No. (%) With Response to Skin Closure
Study 1						
Remifentanil (35)		0.1	0	20 (57%)	33 (94%)	6 (17%)
Remifentanil (35)	Nitrous oxide	0.4	0	3 (9%)†	12 (34%)†	2 (6%)†
Alfentanil (35)		1.0	0	24 (69%)	33 (94%)	12 (34%)
Study 2						
Remifentanil (116)	Isoflurane + nitrous oxide	0.25	35 (30%)†	9 (8%)†	66 (57%)†	19 (16%)
Alfentanil (118)		0.5	12 (10%)	20 (17%)	85 (72%)	25 (21%)
Study 3						
Remifentanil (134)	Propofol	0.5	3 (2%)	14 (11%)†	70 (52%)†	25 (19%)
Alfentanil (66)		2.0	2 (3%)	21 (32%)	47 (71%)	13 (20%)
Study 4						
Remifentanil (98)		0.2	13 (13%)	12 (12%)†	67 (68%)†	7 (7%)
Remifentanil	Isoflurane	0.4	16 (18%)†	4 (4%)†	44 (48%)†	3 (3%)†
Fentanyl		1.5 – 3 microgram/kg pm	7 (7%)	32 (33%)	84 (87%)	11 (11%)

* Not all doses of remifentanil were equipotent to the comparator opioid

† Differences were statistically significant ($p < 0.05$)

In three randomised, controlled studies (n = 407) during general anaesthesia, remifentanil attenuated the signs of light anaesthesia within a median time of 3 to 6 minutes after bolus doses of 1 microgram/kg with or without infusion rate increases of 50% to 100% (up to a maximum rate of 2 microgram/kg/min).

In an additional double-blind, randomised study (n = 103), a constant rate (0.25 microgram/kg/min) of remifentanil was compared to doubling the rate to 0.5 microgram/kg/min approximately 5 minutes before the start of the major surgical stress event. Doubling the rate decreased the incidence of signs of light anaesthesia from 67% to 8% in patients undergoing abdominal hysterectomy, and from 19% to 10% in patients undergoing radical prostatectomy. In patients undergoing laminectomy the lower dose was adequate.

Recovery

In 2,169 patients receiving remifentanil for periods up to 16 hours, recovery from anaesthesia was rapid, predictable, and independent of the duration of the infusion of remifentanil. In the seven controlled, general surgery studies, extubation occurred in a median of 5 minutes (range: -3 to 17 minutes in 95% of patients) in outpatient anaesthesia and 10 minutes (range: 0 to 32 minutes in 95% of patients) in inpatient anaesthesia. Recovery in studies using nitrous oxide or propofol was faster than in those using isoflurane as the concurrent anaesthetic. There was no case of remifentanil-induced delayed respiratory depression (occurring more than 30 minutes after discontinuation of remifentanil).

In a double-blind, randomised study, administration of morphine sulfate (0.15 mg/kg) intravenously 20 minutes before the anticipated end of surgery to 98 patients did not delay recovery of respiratory drive in patients undergoing major surgery with remifentanil-propofol total IV anaesthesia.

Paediatric Anaesthesia

The safety, efficacy and pharmacokinetics of remifentanil have been established in five studies which included 687 paediatric patients (aged 5 days to 17 years). Of these, 437 patients received remifentanil: 65 patients were enrolled in pharmacokinetic studies and 372 paediatric patients were studied undergoing general anaesthesia for routine surgical procedures in the inpatient (n = 190) and outpatient (n = 182) settings. Two hundred and fifty patients were administered comparator anaesthetic regimens. Four of these studies were open-labelled.

One randomised, double-blind, parallel comparator-controlled study consisted of 206 patients, of which 103 received remifentanil. This study found the median time to extubation was 9 minutes vs. 10 minutes for fentanyl. The overall incidences of adverse events were 38% for remifentanil and 39% for fentanyl, drug-related adverse events were 19% and 22% respectively.

The studies confirmed the effectiveness of the initial adult dosing in paediatric patients > 1 year of age with subsequent titration to clinical effect according to individual patient requirements. Remifentanil -based anaesthesia was shown to be as effective as conventional anaesthetic regimens in attenuation of responses to stimulating procedures and the provision of intra-operative haemodynamic stability. Remifentanil could be continued until the end of surgery and recovery from anaesthesia was rapid, predictable and similar to conventional anaesthetic regimens. Generally higher post-operative pain scores were observed when using remifentanil, consistent with the rapid offset of action of remifentanil. This highlights that longer acting analgesia must be established at an appropriate time in advance of the discontinuation of remifentanil to minimise post-operative pain (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Anaesthesia: Dosage in Paediatric Patients (1 – 12 years of age): Guidelines for discontinuation).

No relationship was found between age and the final infusion rate of remifentanil, indicating that the starting dose was appropriate across the range of ages studied. There were no clinically significant differences in time to extubation or other recovery parameters between remifentanil-based anaesthesia and conventional anaesthetic regimens. Remifentanil was well tolerated and the incidence of adverse events at the recommended maintenance doses in combination with inhalational anaesthetics was similar to that reported in adults.

Cardiac Surgery

In preliminary investigations of cardiac anaesthesia, two studies evaluated the pharmacokinetics of remifentanil in patients (n = 25) undergoing hypothermic CABG surgery; and two dose ranging studies were conducted which included a total of 217 ASA II-IV patients undergoing CABG surgery. The data indicated that high dose remifentanil (starting doses 1 – 3 microgram/kg/min) effectively attenuated responses to major surgical stress and was associated with a rapid recovery profile. However, none of these studies included comparator opioids. Subsequently remifentanil was evaluated in four randomised, double blind studies including a total of 830 patients (450 remifentanil, 380 comparator opioid) undergoing coronary artery bypass graft (CABG) or valve replacement/repair surgery. This was initiated to develop dosing guidelines for use of remifentanil in cardiac patients, establish the safety and efficacy of remifentanil compared with the use of fentanyl and sufentanil in 'fast-track' cardiac anaesthesia; and especially in 'higher risk' cardiac patients – those with impaired left ventricular function (ejection fraction < 0.35) or undergoing valve surgery.

A high dose remifentanil-based regimen was generally more effective in attenuating major surgical stress responses compared to conventional opioid regimens (low/medium intermittent dose) used for 'fast-track' cardiac surgery (e.g. attenuation of response to Maximal Sternal Spread was 11 - 21% with remifentanil vs. 44 - 52% fentanyl and 39% sufentanil). Comparable haemodynamic stability was observed during surgery with remifentanil and comparator opioid regimens. After induction and during maintenance, remifentanil was associated with a higher incidence of hypotension or requirement for treatment of excessive anaesthesia than comparator opioid regimens.

Continuation of a remifentanil regimen at a fixed rate of 1 microgram/kg/min into the immediate postoperative period (ICU) was effective in managing patient comfort. The protocol regimen for transition to alternative analgesia in advance of down titration and discontinuation from remifentanil during weaning for extubation, was effective. Although sedation was increased it did not result in significant delay in post-operative recovery. Times to discharge from an intensive care setting were comparable to 'fast-track' opioid regimens.

For the side-effect profile in cardiac surgery, refer to Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Neurosurgery

Remifentanil was administered to 61 patients undergoing craniotomy for removal of a supratentorial mass lesion. In these studies, ventilation was controlled to maintain a predicted $PaCO_2$ of approximately 28 mmHg. In one study (n = 30) with remifentanil and 66% nitrous oxide, the median time to extubation and to patient response to verbal commands was 5 minutes (range -1 to 19 minutes). Intracranial pressure and cerebrovascular responsiveness to carbon dioxide were normal.

A randomised, controlled study compared remifentanil (n = 31) to fentanyl (n = 32). Remifentanil (1 microgram/kg/min) and fentanyl (2 microgram/kg/min) were administered after induction with thiopentone and pancuronium. A similar number of patients (6%) receiving remifentanil and fentanyl had hypotension during induction. Anaesthesia was maintained with nitrous oxide and remifentanil at a mean infusion rate of 0.23 microgram/kg/min (range 0.1 to 0.4) compared with a fentanyl mean infusion rate of 0.04 microgram/kg/min (range 0.02 to 0.07). Supplemental isoflurane was administered as needed. The patients receiving remifentanil required a lower mean isoflurane dose (0.07 MAC-hours) compared with 0.64 MAC-hours for the fentanyl patients (p = 0.04). Remifentanil was discontinued at the end of anaesthesia, whereas fentanyl was discontinued at the time of bone flap replacement (a median time of 44 minutes before the end of surgery). Median time to extubation was similar (5 and 3.5 minutes, respectively, with remifentanil and fentanyl). None of the patients receiving remifentanil required naloxone compared to seven of the fentanyl patients (p = 0.01). Eighty-one percent (81%) of patients receiving remifentanil recovered (awake, alert, and oriented) within 30 minutes after surgery compared with 59% of fentanyl patients (p = 0.06). At 45 minutes, recovery rates were similar (81% and 69% respectively for remifentanil and fentanyl, p = 0.27). Patients receiving remifentanil required an analgesic for headache sooner than fentanyl patients (median of 35 minutes compared with 136 minutes, respectively [p = 0.04]). No adverse cerebrovascular effects were seen in this study.

Intensive Care Unit

Three clinical studies were conducted to determine the safety and efficacy of remifentanil in a clinically relevant intensive care population requiring mechanical ventilation for up to three days. Two of these studies (USA03206 & USA 30207) were randomised, double-blind, controlled, parallel group studies, the third of these (USA 30212) was an open labelled, non-comparator study. A total of 261 patients received remifentanil, 81 received fentanyl and 83 received morphine. Of those receiving remifentanil, 32 were treated for ≥ 48 hours, 12 of whom had moderate/severe renal impairment.

The randomised, double-blind studies compared a remifentanil-based analgesia/sedation regimen with fentanyl- or morphine-based regimens. The opioid was initially titrated to achieve adequate levels for sedation (a patient who was calm, easily rousable and followed commands) and analgesia (no or mild pain). Frequent monitoring of the depth of sedation and analgesia was undertaken. Administration of sedative agent was initiated only if the target level of sedation could not be achieved with opioid alone.

A remifentanil-based regimen was effective in providing optimal sedation for the majority (82% - 90%) of the maintenance phase. Fentanyl and morphine comparator regimens provided similar efficacy in terms of duration of optimal sedation. Remifentanil infusion alone provided optimal sedation in the majority (65% in USA30206, 78% in USA30207 and 43% in USA30212) of patients without the need for a supplementary sedative agent.

The primary end point, between patient variability in the percentage of hours of optimal sedation, was not statistically significantly different for remifentanil compared with fentanyl (study USA30206) or morphine (study USA30207).

Remifentanil was effective in providing adequate analgesia (no pain/mild pain) for the majority (> 94%) of the maintenance phase. Fentanyl and morphine provided similar efficacy in terms of duration of adequate analgesia. Moderate/severe pain was reported in a higher percentage of patients administered remifentanil compared to those administered morphine and fentanyl subsequent to down titration and discontinuation of the opioid. This was consistent with the rapid offset of the analgesic effects of remifentanil. The time to extubation was rapid and comparable between remifentanil and the comparator regimens (median values ≤1.3h in studies USA30206 and USA30207). Remifentanil was associated with acceptable haemodynamic stability during the maintenance phase, which was similar to that observed in patients administered morphine or fentanyl. A greater incidence of haemodynamic changes were reported in the extubation, post-extubation and post-treatment phases in the remifentanil group, which were related to a greater incidence of pain.

The data indicate that a remifentanil-based regimen (starting infusion rate 0.1 - 0.15 microgram/kg/min), was very effective for establishing and maintaining optimal analgesia and sedation in a wide range of IC patients, including those with severe renal impairment. In the majority of patients (≥ 60%) in the comparator studies there was no requirement for infusion of supplementary sedative agents (midazolam or propofol) to maintain optimal sedation (SAS 4). In study USA30212, where patients could be more deeply sedated (SAS 2-4), there was a greater requirement for supplementary use of sedative i.e. 58% of patients required propofol infusion. Use of a remifentanil-based regimen resulted in rapid extubation of the patients, similar to the comparator opioid regimens.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 microgram/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5 ng/mL. Unlike other fentanyl analogues, the duration of action does not increase with prolonged administration. Remifentanil is approximately 70% bound to plasma proteins.

Distribution

The central volume of distribution is 100 mL/kg, and the steady-state volume of distribution is 350 mL/kg.

Metabolism

Remifentanil is an esterase metabolised opioid. It is rapidly and extensively metabolised by non-specific esterases in blood and tissues to the carboxylic acid derivative, GR90291. This metabolite is 4,600 times less active than the parent compound in quantitative EEG analysis of opioid activity.

It is unlikely that there is any clinically significant activity of the metabolite. 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.

Excretion

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes due to redistribution. The terminal half-life of the unchanged drug is 10 to 20 minutes. The average clearance of remifentanil in young healthy adults is 40 mL/min/kg. Clearance generally correlates with total body weight (with the exception of severely obese patients in whom it correlates with ideal body weight).

Additional Pharmacokinetic Information

Placental and Milk Transfer

Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanil and/or its metabolites during growth and development. Remifentanil-related material is transferred to the milk of lactating rats. In a human clinical trial, the concentration of remifentanil in foetal blood was approximately 50% of that in maternal blood. The foetal arterio-venous ratio of remifentanil concentrations was approximately 30% suggesting metabolism of remifentanil in the neonate.

Cardiac Anaesthesia

The clearance of remifentanil is reduced by approximately 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree Celsius.

Pharmacokinetics in Patients with Renal Impairment

After 72 hours of infusion, the rapid recovery from remifentanil-based sedation and analgesia is unaffected by mild renal impairment and may be slightly prolonged in patients with moderate/severe renal impairment (median time to off-set of effects of remifentanil was 30 minutes in patients with moderate/severe renal impairment compared with 13.5 minutes in mild renal impairment).

The pharmacokinetics of remifentanil are not significantly changed in patients with varying degrees of renal impairment even after administration for up to 3 days in the intensive care setting.

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 may exceed 250-fold the level of remifentanil at steady-state in some patients. There is no evidence that the metabolite produces clinically relevant μ-opioid effects even after administration of remifentanil infusions for up to three days in these patients. However, due to the limited data available, it is not known whether the accumulated metabolite has any other clinically relevant effects (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials: Intensive Care Unit).

There is no evidence that remifentanil is extracted during renal replacement therapy.

The carboxylic acid metabolite is extracted during haemodialysis by at least 30%.

Pharmacokinetics in Patients with Hepatic Impairment

The pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Individuals with severe hepatic impairment demonstrated statistically significant, reduced sensitivity to carbon dioxide stimulation of minute ventilation, which may indicate an increased sensitivity 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's need.

Pharmacokinetics in Paediatric Patients

In paediatric patients 5 days to 17 years of age, 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 half-life of remifentanil is not significantly different in neonates suggesting that 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 - 17 years of age are similar to those seen in adults after correcting for differences in body weight.

Pharmacokinetics in Elderly Patients

The clearance of remifentanil is reduced (approximately 25%) in elderly patients (> 65 years) compared to young patients. The pharmacodynamic activity of remifentanil increases with increasing age. The EC50 for formation of delta waves on the electroencephalogram (EEG) in elderly patients receiving remifentanil is 50% lower than in 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's need.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Remifentanil was not mutagenic in bacterial assays for gene mutations (*Salmonella typhimurium* histidine reversion assay), chromosomal aberrations (mouse micronucleus and Chinese hamster ovary chromosome) and a DNA repair assay (rat hepatocytes). However, a positive result was obtained in the mouse lymphoma L5178Y/$tk^{+/-}$ assay in the presence of metabolic activation.

Carcinogenicity

There is no information currently available on the carcinogenic potential of remifentanil.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

REMIFENTANIL VIATRIS contains the following excipients: glycine (as a bulk agent) and hydrochloric acid (for pH adjustment).

6.2 INCOMPATIBILITIES

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Instructions for Use: Physical Incompatibilities.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Store in original container.

The reconstituted solution is chemically and physically stable for 48 hours at room temperature but since the product includes no preservative, from a microbiological point of view, reconstituted 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 would normally not be longer than 24 hours at 2 to 8° C.

REMIFENTANIL VIATRIS is for single use in one patient only. Discard any residue.

Any unused diluted solution should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Type I clear glass vial with a chlorobutyl stopper and a flip-off cap.

Pack sizes: 1 or 5 vials

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 163901– REMIFENTANIL VIATRIS 1mg remifentanil (as hydrochloride) powder for injection vial

AUST R 163902– REMIFENTANIL VIATRIS 2mg remifentanil (as hydrochloride) powder for injection vial

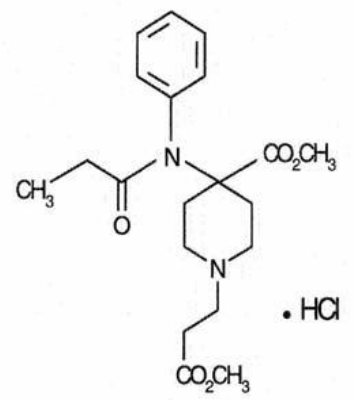
AUST R 163903– REMIFENTANIL VIATRIS 5mg remifentanil (as hydrochloride) powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 1-(2-Methoxycarbonyl-ethyl)-4-(phenylpropionyl-amino)-piperidine-4-carboxylic acid methyl ester hydrochloride

Molecular formula: $C_{20}H_{28}N_2O_5$.HCl

Molecular weight: 412.9

CAS Number

13539-07-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 (Controlled Drug)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

22/12/2010

10 DATE OF REVISION

08/09/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Addition of Sleep-related breathing disorders, Adrenal insufficiency, Endocrine effects, Neonatal withdrawal Syndrome, Gastrointestinal toxicity, headings and information.
4.6	Addition of neonatal withdrawal syndrome information.
4.8	Addition of post-marketing experience.
4.9	Addition of toxic leukoencephalopathy information.

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