

# NEW ZEALAND DATA SHEET

## 1. REMIFENTANIL-AFT powder for injection

Remifentanil-AFT 1 mg powder for injection.

Remifentanil-AFT 2 mg powder for injection.

Remifentanil-AFT 5 mg powder for injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Remifentanil-AFT 1 mg

Each vial contains 1 mg remifentanil (as hydrochloride).

Following reconstitution, the solution contains 1 mg/mL remifentanil (as hydrochloride) if prepared as recommended (see section 6.6).

### Remifentanil-AFT 2 mg

Each vial contains 2 mg remifentanil (as hydrochloride).

Following reconstitution, the solution contains 1 mg/mL remifentanil (as hydrochloride) if prepared as recommended (see section 6.6).

### Remifentanil-AFT 5 mg

Each vial contains 5 mg remifentanil (as hydrochloride).

Following reconstitution, the solution contains 1 mg/mL remifentanil (as hydrochloride) if prepared as recommended (see section 6.6).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for injection.

White to off-white lyophilized powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Remifentanil-AFT is indicated as an analgesic agent:

- for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery
- for the continuation of analgesia in the immediate post-operative period during transition to longer acting analgesia. This should be under close supervision
- for the provision of analgesia and sedation in mechanically ventilated intensive care patients.

## 4.2 Dose and method of administration

### Dose

Remifentanyl-AFT should only be administered by persons specifically trained in the use of anaesthetic agents and the recognition and management of the expected adverse effects of potent opioids including respiratory and cardiac resuscitation. This training must include the establishment and maintenance of a patient airway and assisted ventilation. It should only be administered in a facility equipped for monitoring and support of respiratory and cardiovascular function.

Continuous infusions of Remifentanyl-AFT must be administered by either a calibrated infusion device into a fast-flowing IV line or via a dedicated IV line. The infusion line should be connected at (or close to) the venous cannula and primed, to minimise the potential dead space (see section 6.6 for further information).

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Remifentanyl-AFT after use (see section 4.4).

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

Remifentanyl-AFT is stable for 24 hours when stored at or below 25 °C after reconstitution and further dilution with one of the following IV fluids:

- Sterilised Water for Injections.
- 5% Dextrose Injection.
- 5% Dextrose and 0.9% Sodium Chloride Injection.
- 0.9% Sodium Chloride Injection.
- 0.45% Sodium Chloride Injection.

Refer to section 6.6 for further information, including tables to assist titration of Remifentanyl-AFT according to the patient's anaesthetic needs.

With a manually-controlled infusion, Remifentanyl-AFT may be diluted to concentrations of 20-250 µg/mL. The recommended dilutions are 50 µg/mL for adults and 20-25 µg/mL for paediatric patients aged 1 year and over.

### **General anaesthesia**

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

### ***Adults***

The starting infusion rates and dose ranges are given in the table following:

### Dosing Guidelines for Adults

Indication	Bolus Infusion of Remifentanil-AFT (µg/kg)	Continuous Infusion of Remifentanil-AFT (µg/kg/min)	
		Starting Rate	Range
Induction of anaesthesia in ventilated patients	1 (given over at least 30 seconds)	0.5 – 1	-
Maintenance of anaesthesia in ventilated patients			
Nitrous oxide (66%)	0.5 – 1	0.4	0.1 – 2
Isoflurane (starting dose 0.5 MAC)	0.5 – 1	0.25	0.05 – 2
Propofol (starting dose 100 µg/kg/min)	0.5 – 1	0.25	0.05 – 2
Spontaneous ventilation anaesthesia	Not recommended	0.04	0.025 – 0.1
Continuation of anaesthesia into the immediate post-operative period	Not recommended	0.1	0.025 – 0.2

When given by bolus infusion at induction Remifentanil-AFT should be administered over a period of not less than 30 seconds.

At the above doses, Remifentanil-AFT significantly reduces the amount of hypnotic agent needed to maintain anaesthesia. Isoflurane and propofol should be administered as recommended above to avoid an excessive depth of anaesthesia (refer also 'Concomitant medication' below). Data is not available for dosage recommendations for concurrent use of other hypnotics with remifentanil.

#### *Induction of anaesthesia*

Remifentanil-AFT should be administered with a hypnotic agent, e.g. propofol, thiopentone, isoflurane, for the induction of anaesthesia. It can be administered at an infusion rate of 0.5 – 1 µg/kg/min with or without an initial bolus infusion of 1 µg/kg over at least 30 seconds. A bolus infusion is not necessary if endotracheal intubation is to occur more than 8 to 10 minutes after the start of the infusion.

#### *Maintenance of anaesthesia*

After endotracheal intubation the infusion rate of Remifentanil-AFT should be decreased as indicated in the table above. Because of the fast onset and short duration of action of remifentanil, the rate of administration during anaesthesia may be titrated upward in 25 - 100% increments or downward in 25 - 50% decrements, every 2 - 5 minutes to attain the desired level of µ-opioid response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 – 5 minutes.

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

In spontaneously breathing anaesthetised patients with a secured airway, respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended starting infusion rate for supplemental analgesia, in spontaneously

breathing anaesthetized patients, is 0.04 µg/kg/min titrated to the desired effect. Infusion rates of 0.025 – 0.1 µg/kg/min have been studied. Bolus injections are not recommended in spontaneously breathing anaesthetised patients.

#### *Continuation into the immediate post-operative period*

If longer acting analgesia has not been established prior to the end of surgery, Remifentanil-AFT may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.

In ventilated patients, the infusion rate should continue to be titrated to ensure the desired effect.

In spontaneously breathing patients, the infusion rate should initially be decreased to a rate of 0.1 µg/kg/min. The infusion rate may then be increased or decreased by not more than 0.025 µg/kg/min every 5 minutes, to balance the patient's level of analgesia and respiratory rate.

Remifentanil-AFT should only be used in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, under the close supervision of persons specifically trained in the recognition and management of the respiratory effects of potent opioids.

The use of bolus injections of Remifentanil-AFT to treat post-operative pain is not recommended in patients who are breathing spontaneously.

#### *Guidelines for discontinuation*

Due to the rapid offset of action, no residual opioid activity will be present within 5 - 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to or immediately following discontinuation of Remifentanil-AFT. Sufficient time should be allowed for the longer acting analgesic to reach maximum effect. The choice of analgesic should be appropriate for the surgical procedure and the required level of post-operative care.

#### *Concomitant medication*

Remifentanil-AFT decreases the amount/dose of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).

Doses of isoflurane, thiopentone, propofol and temazepam have been reduced by up to 75% when used concurrently with remifentanil for anaesthesia.

#### ***Paediatric population (1-12 years)***

##### *Induction of anaesthesia*

There are insufficient data to make a dosage recommendation.

##### *Maintenance of anaesthesia*

Dosing guidelines are provided in the table below:

### Dosing Guidelines for Children 1 – 12 years

Concomitant Anaesthetic Agent	Bolus Infusion of Remifentanil-AFT (µg/kg)	Continuous Infusion of Remifentanil-AFT (µg/kg/min)	
		Starting Rate	Range
Nitrous oxide (70%)	1	0.4	0.4 – 3
Halothane (starting dose 0.3 MAC)	1	0.25	0.05 – 1.3
Sevoflurane (starting dose 0.3 MAC)	1	0.25	0.05 – 0.9
Isoflurane (starting dose 0.5 MAC)	1	0.25	0.06 – 0.9

In clinical trials, nitrous oxide/oxygen was administered with either isoflurane, sevoflurane or halothane in a 2:1 ratio.

When given by bolus infusion, Remifentanil-AFT should be administered over at least 30 seconds. Surgery should not start 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. Isoflurane, halothane and sevoflurane should therefore be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics.

#### *Guidelines for discontinuation*

Following discontinuation of the infusion, the offset of the analgesic effect is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be anticipated and implemented (see above 'Adults, Guidelines for discontinuation').

#### *Neonates and infants aged under 1 year*

While the pharmacokinetic profile of remifentanil in neonates and infants aged under 1 year is comparable to that seen in adults after correction for body weight differences, there are insufficient clinical data to make dosage recommendations for this age group.

### Cardiac anaesthesia

#### *Adults*

### Dosing Guidelines for Cardiac Anaesthesia

Indication	Bolus Infusion of Remifentanil-AFT ( $\mu\text{g}/\text{kg}$ )	Continuous Infusion of Remifentanil-AFT ( $\mu\text{g}/\text{kg}/\text{min}$ )	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	
Maintenance of anaesthesia			
Isoflurane (starting dose 0.4 MAC)	0.5 – 1	1	0.003 – 4
Propofol (starting dose 50 $\mu\text{g}/\text{kg}/\text{min}$ )	0.5 – 1	1	0.01 – 4.3
Continuation of post-operative analgesia prior to extubation	Not recommended	1	0 – 1

#### *Induction period of anaesthesia*

Following administration of the hypnotic agent to achieve loss of consciousness, Remifentanil-AFT should be administered at an initial infusion rate of 1  $\mu\text{g}/\text{kg}/\text{min}$ . Use of bolus infusions of Remifentanil-AFT during induction of cardiac surgical patients is not recommended. Endotracheal intubations should not occur until at least 5 minutes after the start of the infusion.

#### *Maintenance period of anaesthesia*

After endotracheal intubation the infusion rate of Remifentanil-AFT should be titrated according to patient need. Supplemental bolus doses may also be given as required.

High risk cardiac patients, e.g. those with poor ventricular function, should be administered a maximum bolus dose of 0.5  $\mu\text{g}/\text{kg}$ . These dosing recommendations also apply during hypothermic cardiopulmonary bypass.

#### *Concomitant medication*

At the doses recommended above, Remifentanil-AFT significantly reduces the amount of hypnotic agent required to maintain anaesthesia. 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.

#### *Continuation of post-operative analgesia prior to extubation*

It is recommended that the infusion of Remifentanil-AFT 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 infusion rate adjusted to meet the individual patient's requirements.

#### *Guidelines for discontinuation*

Prior to discontinuation of Remifentanil-AFT, patients should 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.

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 infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Haemodynamic changes, e.g. hypertension and tachycardia, should be treated with alternative agents as appropriate.

### ***Paediatric population***

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

### **Use in intensive care**

#### ***Adults***

Remifentanil-AFT can initially be used alone to provide analgesia and sedation in mechanically ventilated intensive care patients.

It is recommended that Remifentanil-AFT is initiated at an infusion rate of 0.1 – 0.15 µg/kg/min. The infusion rate should be titrated at, at least 5 minute intervals in increments of 0.025 µg/kg/min to achieve the desired level of analgesia and sedation. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the infusion rate adjusted accordingly. If an infusion rate of 0.2 µg/kg/min is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent be initiated. The dose of the sedative agent should be titrated to obtain the desired level of sedation. Further increases to the remifentanil infusion rate (in increments of 0.025 µg/kg/min) may be made if additional analgesia is required.

The safety and efficacy of remifentanil infusion in mechanically ventilated intensive care patients has been established for up to 3 days. The use of Remifentanil-AFT for longer than 3 days is not recommended.

Starting infusion rates of between 0.1 – 0.15 µg/kg/min with a typical dose range of 0.006 – 0.74 µg/kg/min provide analgesia and sedation.

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

Use of Remifentanil-AFT will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses are given in the table below:

**Recommended Starting Dose of Sedative Agents (if required)**

<b>Sedative agent</b>	<b>Bolus (mg/kg)</b>	<b>Infusion (mg/kg/h)</b>
Propofol	Up to 0.5	0.5
Midazolam	Up to 0.03	0.03

To allow for separate titration of the respective agents, sedative agents should not be given as an admixture.

### *Additional analgesia for ventilated patients undergoing stimulating procedures*

An increase in the existing Remifentanyl-AFT 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 an infusion rate of at least 0.1 µg/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 - 5 minutes in increments of 25 - 50% in anticipation of (or in response to), additional analgesia requirements. A mean infusion rate of 0.25 µg/kg/min (up to a maximum 0.75 µg/kg/min), has been administered to provide additional anaesthesia during stimulating procedures.

### *Guidelines for discontinuation*

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

To ensure a smooth emergence from a remifentanyl-based regimen it is recommended that the infusion rate be titrated in stages to 0.1 µg/kg/min over a period up to 1 hour prior to extubation.

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

### *Paediatric population*

No data available on use in paediatric patients in intensive care.

### *Renal impairment*

No adjustments are required for renally impaired patients in intensive care including those undergoing renal replacement therapy.

### **Dosage adjustments in at-risk groups**

#### *Elderly (over 65 years)*

##### *General anaesthesia*

Due to increased sensitivity to the pharmacological effects the initial starting dose should be half the recommended adult dose which is titrated to individual patient need. This adjustment applies to all phases of anaesthesia including induction, maintenance and immediate post-operative analgesia.

##### *Cardiac anaesthesia*

No initial dose reduction required.

##### *Intensive care*

No initial dose reduction required.

### ***Obese patients***

It is recommended that the dosage be based upon ideal body weight as the clearance and volume of distribution of remifentanil are better correlated with ideal body weight rather than actual body weight in this population.

### ***Renal impairment***

No dosage adjustment is required.

### ***Hepatic impairment***

No initial dosage adjustment is required however patients with severe hepatic impairment should be closely monitored and the dose titrated to individual patient need, as these patients may be more sensitive to the respiratory depressant effects of remifentanil.

### ***Neurosurgery***

Limited clinical experience indicates that there are no special dosage requirements.

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

#### ***General anaesthesia***

The haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients therefore caution is recommended when administering Remifentanil-AFT to these patients. Initial dosage reduction and titration to the desired effect are recommended.

#### ***Cardiac anaesthesia***

No initial dose reduction required.

### **Method of administration**

Intravenous.

For instructions on reconstitution of the medicine before administration, see section 6.6.

## **4.3 Contraindications**

- Epidural and intrathecal use (product contains glycine)
- Patients with known hypersensitivity to the active substance and/or other fentanyl analogues, or to any of the excipients listed in section 6.1.

## **4.4 Special warnings and precautions for use**

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

Remifentanil-AFT is not recommended for use as the sole agent in general anaesthesia.

#### Muscle rigidity - prevention and management

At the recommended doses, muscle rigidity may occur. The incidence of muscle rigidity is related to the dose and rate of administration. Therefore bolus infusions should be administered over at least 30 seconds.

Muscle rigidity induced by Remifentanil-AFT should be treated with appropriate supporting measures taking into account the patient's clinical condition.

Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of Remifentanil-AFT may be resolved by stopping or decreasing the rate of administration of Remifentanil-AFT. Resolution of muscle rigidity after discontinuing the infusion occurs within minutes.

Alternatively an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of Remifentanil-AFT.

#### Respiratory depression

With all potent opioids, profound analgesia is accompanied by marked respiratory depression. Remifentanil-AFT should only be used where facilities for monitoring and resolving respiratory depression are available. Respiratory depression should be managed appropriately, including decreasing the infusion rate by 50% or a temporary discontinuation of the infusion. Unlike other fentanyl analogues remifentanil has not been shown to cause recurrent respiratory depression even after prolonged administration. However, as many factors may affect post-operative recovery it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

#### Cardiovascular effects

Hypotension and bradycardia (see section 4.8) may be managed by either reducing the Remifentanil-AFT infusion rate or the dose of concurrent anaesthetics or by using I.V. fluids, vasopressor or anticholinergic agents as appropriate.

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

#### Rapid offset of action

Due to the very rapid offset of action of Remifentanil-AFT, no residual opioid activity will be present within 5-10 minutes after the discontinuation of Remifentanil-AFT. For patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to or immediately following discontinuation of Remifentanil-AFT. 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 post-operative care.

#### Discontinuation of treatment

Tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, especially after prolonged administration of remifentanil. Re-introduction and tapering of the infusion has been beneficial.

#### Inadvertent administration

A sufficient amount of Remifentanil-AFT may be present in the dead space of the I.V. line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with I.V. fluids or other medicines. This may be avoided by administering Remifentanil-AFT into a fast-flowing I.V. line or via a dedicated I.V. line which is adequately cleared of residual medicine or which is removed upon discontinuation of Remifentanil-AFT.

#### Drug abuse

Dependency may occur with remifentanil.

#### Concomitant use with benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Remifentanil-AFT with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see section 4.5).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Remifentanil-AFT is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance

use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see section 4.5).

#### **4.5 Interaction with other medicines and other forms of interaction**

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

The cardiovascular effects of remifentanyl, e.g. hypotension and bradycardia, may be exacerbated in patients receiving concomitant cardiac depressant medicines, such as beta-blockers and calcium channel blocking agents.

Like other opioids, remifentanyl decreases the amount and/or dose of inhaled and I.V. anaesthetics, and benzodiazepines required for anaesthesia. If doses of concomitantly administered CNS depressant medicines are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.

##### Use with benzodiazepines and other CNS depressants

Clinical impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4).
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Category C

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

The safe use of Remifentanyl-AFT during labour and/or delivery has not been established. There are insufficient data to recommend its use during labour or caesarean section.

Remifentanyl crosses the placental barrier and fentanyl analogues may cause respiratory depression in the infant.

### Breastfeeding

It is not known if remifentanil is excreted in breast milk. However, as fentanyl analogues are excreted in breast milk and animal studies have indicated that remifentanil is excreted in rat milk, caution should be taken when remifentanil is administered to nursing mothers.

### Fertility

For a summary of the reproductive toxicity study findings, please refer to section 5.3.

## **4.7 Effects on ability to drive and use machines**

Patients should be advised not to drive or operate machinery after having had remifentanil administered.

## **4.8 Undesirable effects**

The most common adverse effects associated with Remifentanil-AFT are those associated with  $\mu$ -opioid agonist pharmacology. The adverse effects typically resolve within minutes of discontinuing or decreasing the rate of Remifentanil-AFT administration.

Adverse effects are given below by system organ and frequency. Frequencies below are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

### Immune system disorders

Rare: Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents.

### Nervous system disorders

Very common: Skeletal muscle rigidity

Rare: Sedation (during recovery from general anaesthesia)

Not known: Convulsions

### Cardiac disorders

Common: Bradycardia

Rare: Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents.

Not known: Atrioventricular block

### Vascular disorders

Very common: Hypotension

Common: Post-operative hypertension

#### Respiratory, thoracic and mediastinal disorders

Common:	Acute respiratory depression, apnoea
Uncommon:	Hypoxia

#### Gastrointestinal disorders

Very common:	Nausea, vomiting
Uncommon:	Constipation

#### Skin and subcutaneous tissue disorders

Common:	Pruritus
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#### General disorders and administration site conditions

Common:	Post-operative shivering
Uncommon:	Post-operative aches
Not known	Drug tolerance

#### Discontinuation of treatment

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

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

### **4.9 Overdose**

Overdose symptoms are an extension of the pharmacologically predictable actions of remifentanyl.

Due to the very short duration of action, the potential for deleterious effects due to overdose are limited to the immediate time period following medicine administration. Response to discontinuation of the medicine is rapid with return to baseline within 10 minutes.

In the event of overdose or suspected overdose:

- discontinue administration
- maintain a patent airway
- initiate assisted or controlled ventilation with oxygen
- 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 vasopressors for the treatment of hypotension and other supportive measures may be required. The duration of respiratory

depression following overdose is unlikely to exceed the duration of action of the opioid antagonist.

I.V. administration of an opioid antagonist, e.g. naloxone, may be given as a specific antidote to manage severe respiratory depression and muscle rigidity.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH06.

Remifentanyl is a selective  $\mu$ -opioid agonist with a rapid onset and very short duration of action. The  $\mu$ -opioid activity of remifentanyl is antagonised by narcotic antagonists, e.g. naloxone.

Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after administration of bolus doses of remifentanyl of up to 30  $\mu$ g/kg.

### **5.2 Pharmacokinetic properties**

#### Absorption

Blood concentrations of remifentanyl are dose proportional throughout the recommended dose range. For every 0.1  $\mu$ g/kg/min increase in infusion rate, the blood concentration of remifentanyl will increase 2.5 ng/mL.

#### Distribution

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

#### Biotransformation

Remifentanyl is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanyl results in the formation of an essentially inactive carboxylic acid metabolite. The half-life of the metabolite in healthy adults is 2 hours. Approximately 95% of remifentanyl is recovered in the urine as the carboxylic acid metabolite. Remifentanyl is not a substrate for plasma cholinesterase.

#### Elimination

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

#### Special populations

### ***Cardiac anaesthesia***

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

### ***Renal impairment***

The rapid recovery from remifentanyl-based sedation and analgesia appears unaffected by renal status.

The pharmacokinetics of remifentanyl 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 remifentanyl at steady-state in some patients. Clinical data indicates that accumulation of the metabolite does not result in clinically relevant  $\mu$ -opioid effects, even after administration of remifentanyl infusions for up to 3 days in these patients.

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

At least 30% of the carboxylic acid metabolite is removed during haemodialysis.

### ***Hepatic impairment***

The pharmacokinetics of remifentanyl is not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanyl. These patients should be closely monitored and the dose of remifentanyl titrated to the individual patient need.

### ***Paediatric patients***

In paediatric patients aged 5 days to 17 years, the average clearance and steady state volume of distribution of remifentanyl are increased in younger children but decline to young healthy adult values by age 17 years.

The half-life of remifentanyl is not significantly different in neonates, suggesting that changes in analgesic effect after changes in infusion rate of remifentanyl should be rapid and similar to that seen in young healthy adults.

The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2-17 years of age are similar to those seen in adults after correcting for body weight.

### ***Elderly***

The clearance of remifentanyl is reduced by approximately 25% in patients aged over 65 years when compared to young patients. The pharmacodynamic activity of remifentanyl increases with increasing age.

Elderly patients have a remifentanil EC<sub>50</sub> for formation of delta waves on the electroencephalogram (EEG) that is 50% lower than young patients. Therefore, the initial dose of remifentanil should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

#### ***Placental and milk transfer***

In a human clinical trial, the 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.

### **5.3 Preclinical safety data**

Remifentanil, like some other fentanyl analogues, produced increases in action potential duration (APD) in dog isolated Purkinje fibres. There were no effects at a concentration of 0.1 micromolar (38 ng/ml). Effects were seen at a concentration of 1 micromolar (377 ng/ml), and were statistically significant at a concentration of 10 micromolar (3770 ng/mL). These concentrations are 12-fold and 119-fold respectively the highest likely free concentrations (or 3-fold and 36- fold respectively, the highest likely whole blood concentrations) following the maximum recommended therapeutic dose.

#### **Acute toxicity**

Expected signs of  $\mu$ -opioid intoxication were observed in non-ventilated mice, rats, and dogs after large single bolus intravenous doses of remifentanil. In these studies, the most sensitive species, the male rat, survived following administration of 5 mg/kg.

Hypoxia-induced brain microhaemorrhages observed in dogs were reversed within 14 days after completion of dosing.

#### **Repeat dose toxicity**

Bolus doses of remifentanil administered to non-ventilated rats and dogs resulted in respiratory depression in all dose groups, and in reversible brain microhaemorrhages in dogs. Subsequent investigations showed that the microhaemorrhages resulted from hypoxia and were not specific to remifentanil. Brain microhaemorrhages were not observed in infusion studies in non-ventilated rats and dogs because these studies were conducted at doses that did not cause severe respiratory depression.

It is to be derived from preclinical studies that respiratory depression and associated sequelae are the most likely cause of potentially serious adverse events in humans.

Intrathecal administration to dogs of the glycine formulation alone (i.e. without remifentanil) caused agitation, pain and hind limb dysfunction and incoordination. These effects are believed to be secondary to the glycine excipient. Because of the better buffering properties of blood, the more rapid dilution, and the low glycine concentration of the remifentanil formulation, this finding has no clinical relevance for intravenous administration of remifentanil.

### Reproductive toxicity studies

Remifentanyl reduced fertility in male rats after daily injection for at least 70 days. A no-effect dose was not demonstrated. Fertility was not affected in female rats. Teratogenic effects were not seen in rats or rabbits. Administration of remifentanyl to rats throughout late gestation and lactation did not significantly affect the survival, development, or reproductive performance of the F1 generation.

### Genotoxicity

Remifentanyl did not yield positive findings in a series of *in vitro* and *in vivo* genotoxicity tests, except in the *in vitro* mouse lymphoma tk assay, which gave a positive result with metabolic activation. Since the mouse lymphoma results could not be confirmed in further *in vitro* and *in vivo* tests, treatment with remifentanyl is not considered to pose a genotoxic hazard to patients.

### Carcinogenicity

Long-term carcinogenicity studies were not performed.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Glycine

Hydrochloric acid (for pH adjustment)

### **6.2 Incompatibilities**

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

It should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Dextrose Injection.

Remifentanyl-AFT should not be mixed with propofol in the same I.V. admixture solution.

Administration of Remifentanyl-AFT into the same I.V. line with blood/serum/plasma is not recommended. Non-specific esterase in blood products may cause the hydrolysis of remifentanyl to its inactive metabolite.

Remifentanyl-AFT should not be mixed with other therapeutic agents prior to administration.

### **6.3 Shelf life**

#### Remifentanyl-AFT 1 mg

Powder: 18 months.

Reconstituted solution: Remifentanyl-AFT is chemically and physically stable for 24 hours after reconstitution when stored below 25 °C, but as it does not contain any antimicrobial preservative, it

should be used as soon as practicable after reconstitution. If the product is not used immediately after reconstitution it should be kept under refrigeration (2 – 8 °C) for not more than 24 hours.

#### Remifentanil-AFT 2 mg

Powder: 24 months.

Reconstituted solution: Remifentanil-AFT is chemically and physically stable for 24 hours after reconstitution when stored below 25 °C, but as it does not contain any antimicrobial preservative, it should be used as soon as practicable after reconstitution. If the product is not used immediately after reconstitution it should be kept under refrigeration (2 – 8 °C) for not more than 24 hours.

#### Remifentanil-AFT 5 mg

Powder: 36 months.

Reconstituted solution: Remifentanil-AFT is chemically and physically stable for 24 hours after reconstitution when stored below 25 °C, but as it does not contain any antimicrobial preservative, it should be used as soon as practicable after reconstitution. If the product is not used immediately after reconstitution it should be kept under refrigeration (2 – 8 °C) for not more than 24 hours.

### **6.4 Special precautions for storage**

Powder: Store below 25 °C.

For storage conditions after reconstitution of the medicine, see section 6.3.

### **6.5 Nature and contents of container**

Remifentanil-AFT is supplied in colourless glass vials with a chlorobutyl stopper and flip-off cap, in packs of 5 vials.

### **6.6 Special precautions for disposal and other handling**

Remifentanil-AFT is stable for 24 hours at 25 °C after reconstitution (storing in a refrigerator is recommended as the product does not contain an anti-microbial preservative) and further dilution to 20 – 250 µg/mL (50 µg/mL is the recommended dilution for adults and 20-25 mcg/mL for paediatric patients aged 1 year and over) with one of the following IV fluids:

- Sterilised Water for Injections.
- 5% Dextrose Injection.
- 5% Dextrose and 0.9% Sodium Chloride Injection.
- 0.9% Sodium Chloride Injection.
- 0.45% Sodium Chloride Injection.

Remifentanil-AFT is compatible with the following I.V. fluids when administered into a running I.V. infusion:

- Lactated Ringer's Injection.

- Lactated Ringer's and 5% Dextrose Injection

Remifentanil-AFT is compatible with propofol when administered into a running I.V. infusion. Infusion rate guidelines for Remifentanil-AFT are given in the following tables:

**Remifentanil-AFT Infusion Rates (mL/kg/h)**

Drug Delivery Rate (µg/kg/min)	Infusion delivery Rate (mL/kg/h) for solution concentrations of			
	20 µg/mL 1 mg/50 mL	25 µg/mL 1 mg/40 mL	50 µg/mL 1 mg/20 mL	250 µg/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

**Remifentanil-AFT Infusion Rates (mL/h) for a 20 µg/mL Solution**

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

**Remifentanil-AFT Infusion Rates (mL/h) for a 25 µg/mL Solution**

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

**Remifentanil-AFT Infusion Rates (mL/h) for a 50 µg/mL Solution**

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

### Remifentanil-AFT Infusion Rates (mL/h) for a 250 µg/mL Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)							
	30	40	50	60	70	80	90	100
0.1	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40
0.15	1.08	1.44	1.80	2.16	2.52	2.88	3.24	3.60
0.2	1.44	1.92	2.40	2.88	3.36	3.84	4.32	4.80
0.25	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
0.5	3.60	4.80	6.00	7.20	8.40	9.60	10.80	12.00
0.75	5.40	7.20	9.00	10.80	12.60	14.40	16.20	18.00
1.0	7.20	9.60	12.00	14.40	16.80	19.20	21.60	24.00
1.25	9.00	12.00	15.00	18.00	21.00	24.00	27.00	30.00
1.5	10.80	14.40	18.00	21.60	25.20	28.80	32.40	36.00
1.75	12.60	16.80	21.00	25.20	29.40	33.60	37.80	42.00
2.0	14.40	19.20	24.00	28.80	33.60	38.40	43.20	48.00

## 7. MEDICINE SCHEDULE

Class B3 Controlled Drug.

## 8. SPONSOR

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## 9. DATE OF FIRST APPROVAL

2 June 2011

## 10. DATE OF REVISION OF THE TEXT

October 2020

Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
6.3	Shelf-life of Remifentanil-AFT 2 mg updated

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