

NEW ZEALAND DATA SHEET

Remifentanil-AFT

Remifentanil (as the hydrochloride) 1 mg, 2 mg and 5 mg

Presentation

Remifentanil-AFT, powder for injection, is a white to off-white lyophilised powder for intravenous administration which needs to be reconstituted before use. After reconstitution the solutions are clear and colourless and contain 1 mg/mL if prepared as recommended.

Remifentanil-AFT 1 mg contains 1.097 mg remifentanil hydrochloride in a glass vial with a white flip-off cap.

Remifentanil-AFT 2 mg contains 2.194 mg remifentanil hydrochloride in a glass vial with a green flip-off cap.

Remifentanil-AFT 5 mg contains 5.485 mg remifentanil hydrochloride in a glass vial with a red flip-off cap.

Indications

- 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.

Dosage and Administration

Remifentanil-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 Remifentanil-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 Instructions for Use for further information).

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

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

Remifentanil-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 Instructions for use for further information, including tables to assist titration of Remifentanil-AFT according to the patient's anaesthetic needs.

With a manually-controlled infusion, Remifentanil-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 Remifentanil-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 anaesthetised patients, is 0.04 $\mu\text{g}/\text{kg}/\text{min}$ titrated to the desired effect. Infusion rates of 0.025 - 0.1 $\mu\text{g}/\text{kg}/\text{min}$ 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 $\mu\text{g}/\text{kg}/\text{min}$. The infusion rate may then be increased or decreased by not more than 0.025 $\mu\text{g}/\text{kg}/\text{min}$ 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 Interactions).

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

Children (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 (µg/kg)	Continuous Infusion of Remifentanil-AFT (µg/kg/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 µg/kg/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 µg/kg/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 µg/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.

Children

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)

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

To allow 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 Remifentanil-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 Remifentanil-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 remifentanil-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.

Children

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 remifentanyl 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 remifentanyl.

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 Remifentanyl-AFT to these patients. Initial dosage reduction and titration to the desired effect are recommended.

Cardiac Anaesthesia

No initial dose reduction required.

Contraindications

- Epidural and intrathecal use (product contains glycine)

- Patients with known hypersensitivity to any component of the product and/or other fentanyl analogues.

Warnings and Precautions

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-AF 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 Adverse Effects) 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-AF. 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 remifentanyl. Re-introduction and tapering of the infusion has been beneficial.

Inadvertent administration

A sufficient amount of Remifentanyl-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 Remifentanyl-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 Remifentanyl-AFT.

Drug abuse

Dependency may occur with remifentanyl.

Use during Pregnancy and Lactation

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.

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

Effects on ability to drive and use machines

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

Adverse Effects

The most common adverse effects associated with Remifentanyl-AFT are those associated with μ -opioid agonist pharmacology. The adverse effects typically resolve within minutes of discontinuing or decreasing the rate of Remifentanyl-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 ($< 1/10,000$).

Immune System Disorders

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

Nervous System Disorders

Very common: Skeletal muscle rigidity

Rare: Sedation (during recovery from general anaesthesia)

Cardiac Disorders

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

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

General Disorders and Administration Site Conditions

Common: Post-operative shivering
Uncommon: Post-operative aches

Tachycardia, hypertension and agitation have been reported infrequently following withdrawal of remifentanyl, especially after prolonged administration.

Interactions

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

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.

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.

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.

Further Information

Actions

Remifentanyl is a selective μ -opioid agonist with a rapid onset and very short duration of action. The μ -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 $\mu\text{g}/\text{kg}$.

Pharmacokinetics

Absorption

Blood concentrations of remifentanyl are dose proportional throughout the recommended dose range. For every 0.1 $\mu\text{g}/\text{kg}/\text{min}$ 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.

Metabolism

Remifentanyl is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanyl results in the formation of an essentially inactive carboxylic acid metabolite. 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.

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 μ -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 remifentanyl EC_{50} for formation of delta waves on the electroencephalogram (EEG) that is 50% lower than young patients. Therefore, the initial dose of remifentanyl should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

Placental and milk transfer

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

Other

Remifentanyl-AFT also contains glycine (15 mg) and hydrochloric acid for pH adjustment.

Pharmaceutical Precautions

Instructions for Handling

Remifentanyl-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 μ g/mL (50 μ g/mL is the recommended

dilution for adults and 20-25mcg/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

Incompatibilities

Remifentanil-AFT should only be admixed with the recommended infusion solutions (see Instructions for Handling above). It should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Dextrose Injection.

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

Administration of Remifentanil-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 remifentanil to its inactive metabolite.

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

Shelf life

While Remifentanil-AFT is chemically and physically stable for 24 hours after reconstitution when stored below 25 °C, it does not contain any antimicrobial preservative and 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.

Special Precautions for Storage

Store below 25 °C.

Store reconstituted solution at 2 – 8 °C for not more than 24 hours.

Package Quantities

Remifentanil-AFT 1 mg: Packs of 5 vials

Remifentanil-AFT 2 mg: Packs of 5 vials

Remifentanil-AFT 5 mg: Packs of 5 vials

Medicines Schedule

Controlled Drug B3

Sponsor Details

AFT Pharmaceuticals Ltd

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Date of Preparation

14 June 2011