PROFESSIONAL INFORMATION

ALTIREM IV RANGE

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

ALTIREM IV 1 mg powder for solution for infusion/injection

ALTIREM IV 2 mg powder for solution for infusion/injection

ALTIREM IV 5 mg powder for solution for infusion/injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The reconstituted solutions of ALTIREM IV contain 1 mg per ml of remifentanil as remifentanil hydrochloride.

ALTIREM IV 1 mg: Each single dose vial contains remifentanil hydrochloride equivalent to 1 mg remifentanil.

ALTIREM IV 2 mg: Each single dose vial contains remifentanil hydrochloride equivalent to 2 mg remifentanil.

ALTIREM IV 5 mg: Each single dose vial contains remifentanil hydrochloride equivalent to 5 mg remifentanil.

Sugar free. Preservative free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion or injection.

ALTIREM IV is a sterile, endotoxin-free, preservative free, white to off-white, lyophilised powder, to be reconstituted before intravenous (IV) administration.

After reconstitution, solutions of ALTIREM IV are clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALTIREM IV is indicated as a narcotic analgesic or adjuvant for use during induction and/or maintenance of inhalational anaesthesia during surgical procedures, including cardiac surgery.

ALTIREM IV is indicated for the provision of analgesia and as an aid to sedation (up to 72 hours sedation) in mechanically ventilated intensive care patients. Safety and efficacy beyond 72 hours have not been demonstrated.

4.2 Posology and method of administration

ALTIREM IV should be administered only 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 as the establishment and maintenance of a patent airway and assisted ventilation.

Posology

GENERAL ANAESTHESIA

The administration of ALTIREM IV must be individualised based on the patient's response.

Adults

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

Dosage guidelines for adults

Indication	Bolus infusion of ALTIREM IV (µg/kg)	Continuous infusion of ALTIREM IV (µg/kg/min)	
		Starting rate	Range

With induction of anaesthesia in ventilated patients	1 (given over not less than 30 seconds)	0,5 - 1,0	-
Maintenance of anaesthesia in ventilated patients			
Isoflurane (starting dose 0,5 MAC (minimum alveolar concentration))	0,5 - 1,0	0,25	0,05 - 0,5
Propofol (starting dose 100 µg/kg/min)	0,5 - 1,0	0,25	0,05 - 0,5

At the doses recommended, ALTIREM IV significantly reduced the amount of hypnotic medicine required to maintain anaesthesia. Therefore, isoflurane should be administered as recommended above to avoid excessive depth of anaesthesia (see section 4.5).

Induction of anaesthesia

ALTIREM IV should be administered with a hypnotic medicine, such as isoflurane, for the induction of anaesthesia. ALTIREM IV should be administered at an infusion rate of 0,5 - 1,0 µg/kg/min with or without an initial bolus infusion of 1 µg/kg over not less than 30 seconds. If endotracheal intubation is to occur more than 8 - 10 minutes after the start of the ALTIREM IV infusion, then a bolus infusion is not necessary.

Maintenance of anaesthesia

After endotracheal intubation, the infusion rate of ALTIREM IV should be decreased, according to the anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of ALTIREM IV, the rate of administration during anaesthesia can be titrated upward in 25 -

100 % increments or downward in 25 - 50 % decrements, every 2 - 5 minutes to obtain the desired level of μ-opioid receptor response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 - 5 minutes. The use of ALTIREM IV to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

Guidelines for discontinuation

Due to the very rapid offset of action of remifentanil as in ALTIREM IV, residual opioid activity will be reduced 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 ALTIREM IV. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care.

Concomitant medication

ALTIREM IV decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).

Paediatric patients (1 - 12 years of age)

Induction of anaesthesia

ALTIREM IV is not recommended for the induction of anaesthesia, as insufficient data are available.

Maintenance of anaesthesia

Dosing guidelines for maintenance of anaesthesia in paediatric patients (1 - 12 years of age) (see Table 1 below).

Table 1: Dosing guidelines for maintenance of anaesthesia in paediatric patients (1 - 12 years of age)		
Concomitant anaesthetic	**Bolus infusion**	**Continuous infusion of ALTIREM IV**

medicine	**of ALTIREM IV (µg/kg)**	**(µg/kg/min)**	
		Starting rate	**Typical maintenance rates**
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 - 0,09

When given by bolus infusion, ALTIREM IV should be administered over not less than 30 seconds. Surgery should not commence until at least 5 minutes after the start of ALTIREM IV 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 medicine 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.

Guidelines for discontinuation

Following discontinuation of the infusion, the offset of analgesic effect of ALTIREM IV is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be

anticipated and implemented (see Adults – Guidelines for discontinuation).

Neonates/infants (aged less than 1 year)

The pharmacokinetic profile of remifentanil in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction of body weight differences. However, there are insufficient clinical data to make dosage recommendations for this age group.

CARDIAC ANAESTHESIA

Adults (see Table 2 below)

Table 2: Cardiac anaesthesia

Adults: Dosing guidelines for cardiac anaesthesia

Indication	**Bolus infusion of ALTIREM IV (µg/kg)**	**Continuous infusion of ALTIREM IV (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,	Not recommended	1	0 - 1

prior to extubation			

Induction period of anaesthesia

After administration of a hypnotic medicine to achieve loss of consciousness, ALTIREM IV should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus infusions of ALTIREM IV during induction in cardiac surgical patients is not recommended. Endotracheal intubation 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 ALTIREM IV 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 µg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see section 5.2 – Cardiac anaesthesia).

Concomitant medication

At the doses recommended above, ALTIREM IV significantly reduces the amount of hypnotic medicine 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 ALTIREM IV.

Continuation of post-operative analgesia prior to extubation

It is recommended that the infusion of ALTIREM IV 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 infusion should be maintained initially at a rate of 1 µg/kg/min until the patient is ready to be weaned from the ventilator.

Guidelines for discontinuation

Prior to discontinuation of ALTIREM IV, patients must be given alternative analgesic and sedative medicine at a sufficient time in advance. The choice and dose of medicine(s) should be appropriate for the patient's level of post-operative care. It is recommended that the ALTIREM IV infusion is discontinued by reducing the infusion rate in three to four steps of 50 % at 10 minute intervals. During weaning from the ventilator, the ALTIREM IV 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 medicines, as appropriate.

Paediatric patients

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

USE IN INTENSIVE CARE

ALTIREM IV can be used for the provision of analgesia for up to 72 hours and as an aid to short-term sedation in mechanically ventilated intensive care patients.

It is recommended that ALTIREM IV is initiated at an infusion rate of 0,1 µg/kg/min (6 µg/kg/h) - 0,15 µg/kg/min (9 µg/kg/h). The infusion rate should be titrated in increments of 0,025 µg/kg/min (1,5 µg/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia should be carefully monitored, regularly reassessed and the ALTIREM IV infusion rate adjusted accordingly. If an infusion rate of 0,2 µg/kg/min (12 µg/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative medicine is initiated (see below). The dose of sedative medicine should be titrated to obtain the desired level of sedation.

Further increases to the ALTIREM IV infusion rate in increments of 0,025 µg/kg/min (1,5 µg/kg/h) may be made if additional analgesia is required.

Table 3 summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients:

Table 3: Dosing guidelines for use of ALTIREM IV within the intensive care setting	
Continuous infusion µg/kg/min (µg/kg/h)	
Starting rate	**Range**
0,1 (6) - 0,15 (9)	0,006 (0,36) - 0,74 (44,4)

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

The use of ALTIREM IV will reduce the dosage requirements of any concomitant sedative medicine by approximately 50 %.

Typical starting doses for sedative medicine, if required are given in Table 4 below.

Table 4: Recommended starting dose of sedative medicines, if required		
Sedative medicine	**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 medicines, sedative medicines should not be administered as an admixture.

Additional analgesia for ventilated patients undergoing stimulating procedures

An increase in the existing ALTIREM IV 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 ALTIREM IV infusion rate of at least 0,1 µg/kg/min (6 µg/kg/h) 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 requirement for analgesia. A mean infusion rate of 0,25 µg/kg/min (15 µg/kg/h), maximum 0,75 µg/kg/min (45 µg/kg/h), has been

administered for provision of additional anaesthesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of ALTIREM IV

Due to the very rapid offset of action of ALTIREM IV, no residual opioid activity will be present within 5 - 10 minutes after discontinuation regardless of the duration of infusion. Prior to discontinuation of ALTIREM IV, patients must be given alternative analgesic and sedative medicines at a sufficient time in advance, to allow the therapeutic effects of these medicines to become established. It is therefore recommended that the choice of medicine(s), the dose and the time of administration, are planned prior to discontinuation of ALTIREM IV.

Guidelines for extubation and discontinuation of ALTIREM IV

In order to ensure a smooth emergence from an ALTIREM IV-based regimen, it is recommended that the infusion rate of ALTIREM IV is titrated in stages to 0,1 µg/kg/min (6 µg/kg/h) over a period up to 1 hour prior to extubation. Following extubation, the infusion rate should be reduced by 25 % decrements in at least 10 minute intervals until the infusion is discontinued. During weaning from the ventilator, the ALTIREM IV infusion should not be increased, and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of ALTIREM IV, the IV cannula should be cleared or removed to prevent subsequent inadvertent administration. When other opioid medicines are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing adequate analgesia must always be balanced against the potential risk of respiratory depression with these medicines.

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.

Special populations

Elderly (over 65 years of age)

General anaesthesia

The initial starting dose of ALTIREM IV 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 above Cardiac Anaesthesia: Dosing guidelines).

Intensive care

No initial dose reduction is required (see Use in intensive care).

Obese patients

For obese patients (greater than 30 % over their ideal body weight) the dosage of ALTIREM IV 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.

Renal impairment

No dosage adjustment is necessary in patients with impaired renal function, including intensive care patients.

Hepatic impairment

No dosage adjustment is necessary. However, patients with severe hepatic impairment may be more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely

monitored and the dose of ALTIREM IV titrated to individual patient need.

Neurosurgery

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

ASA (American society of anesthesiologists) 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 ALTIREM IV in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

Cardiac anaesthesia

No initial dose reduction is required (see Cardiac Anaesthesia: Dosing guidelines).

Long-term use in the intensive care unit (ICU)

No data are available on the long-term (longer than 72 hours) use of ALTIREM IV in ICU patients.

Method of administration

After reconstitution, solutions of ALTIREM IV are clear and colourless.

Continuous infusion of ALTIREM IV must be administered by a calibrated infusion device into a fast-flowing IV line or via a dedicated IV line. This infusion line should be connected at, or close to, the venous cannula and primed, to minimise the potential dead space.

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

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

Refer to section 6.6 for reconstitution instruction and further handling.

4.3 Contraindications

As glycine is present in the formulation, ALTIREM IV is contraindicated for epidural and intrathecal use.

- hypersensitivity to remifentanil, other fentanyl analogues or to any of the ingredients of ALTIREM IV listed in section 6.1
- safety in pregnancy and lactation has not been established
- ALTIREM IV should not be used with nitrous oxide and oxygen alone, at altitudes above sea level
- ALTIREM IV should not be used unless artificial ventilation is planned.

4.4 Special warnings and precautions for use

ALTIREM IV is not recommended for use as the sole medicine in general anaesthesia.

ALTIREM IV should be administered only 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 as the establishment and maintenance of a patent airway and assisted ventilation.

The use of ALTIREM IV in mechanically ventilated intensive care patients is not recommended for a duration of treatment greater than 3 days.

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

Interference with daily activities may continue for up to 24 hours and no legal/contractual decisions should be entered into for 24 hours after receiving anaesthetic/conscious sedation. Alcohol use should also be avoided for the same time period.

Rapid offset of action/ transition to alternative analgesia:

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

The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in the intensive care unit. Prior to discontinuation of ALTIREM IV, patients must be given alternative analgesic and sedative medicines.

Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient's surgical procedure and the level of post-operative care anticipated.

When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines:

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

treatment should be as short as possible.

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

Discontinuation of treatment

Symptoms following withdrawal of remifentanil as in ALTIREM IV including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. The use of ALTIREM IV in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

Inadvertent administration

A sufficient amount of remifentanil as in ALTIREM IV 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 medicines. This may be avoided by administering ALTIREM IV into a fast-flowing IV line or via a dedicated IV line, which is adequately cleared of residual medicine, or which is removed upon discontinuation of ALTIREM IV.

Muscle rigidity: prevention and management

At the doses of remifentanil as in ALTIREM IV recommended, muscle rigidity may occur. The incidence is related to the dose and rate of administration. Therefore, bolus infusions should be administered over not less than 30 seconds.

Muscle rigidity induced by remifentanil as in ALTIREM IV must be treated in the context of the patient's clinical condition with appropriate supporting measures including ventilatory support. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking medicine and/or additional hypnotic medicines.

Muscle rigidity seen during the use of remifentanil as in ALTIREM IV as an analgesic may be treated

by stopping or decreasing the rate of administration of ALTIREM IV.

Resolution of muscle rigidity after discontinuing the infusion of ALTIREM IV occurs within minutes. Alternatively, an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of remifentanil.

Respiratory depression: management

Analgesia is accompanied by marked respiratory depression. Therefore, ALTIREM IV should only be used in areas where facilities for monitoring and dealing with respiratory depression are available. The appearance of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50 % or a discontinuation of the infusion. 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 that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area. Patients with impaired lung function and with severe hepatic impairment are more sensitive to the respiratory depressant effects.

Cardiovascular effects

Hypotension and bradycardia, which can give rise to asystole and cardiac arrest (see section 4.5 and section 4.8), may be managed by reducing the rate of infusion of ALTIREM IV or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic medicines as appropriate. Debilitated, hypovolaemic and elderly patients are more sensitive to the cardiovascular effects of remifentanil, as in ALTIREM IV.

Serotonin syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of remifentanil with serotonergic medicines. Serotonergic medicines include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, medicines that affect the

serotonergic neurotransmitter system, and medicines that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. If serotonin syndrome is suspected, rapid discontinuation of remifentanil should be considered.

Dependency

As with other opioids, remifentanil as in ALTIREM IV may produce dependency. There is an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.

Paediatric population

There is limited data available on use in neonates/infants under 1 year of age.

4.5 Interaction with other medicines and other forms of interaction

CNS depressant medicine

Remifentanil as in ALTIREM IV is not metabolised by plasma cholinesterase and therefore interactions with medicines metabolised by the enzyme are not anticipated. Remifentanil decreases the doses of inhaled and IV anaesthetics and benzodiazepines required for anaesthesia.

If doses of concomitantly administered central nervous system (CNS) depressant medicines such as alcohol, anaesthetics, anxiolytics, hypnotics, or antipsychotics are not reduced, patients may experience an increased incidence of adverse effects associated with these medicines.

Other opioids

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

Cardiac depressant medicine, (e.g., beta-blockers and calcium channel blocking agents)

The cardiovascular effect of remifentanil as in ALTIREM IV (hypotension and bradycardia) may be exacerbated in patients receiving concomitant cardiac depressant medicines, such as beta blockers and calcium channel blocking medicines.

Serotonergic medicine

Co-administration of remifentanil such as ALTIREM IV with medicine that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome, a potentially life-threatening condition. Serotonergic medicines include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, medicine that effect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol) and monoamine oxidase (MAO) inhibitors.

Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to remifentanil use.

Alcohol

After receiving ALTIREM IV, it is advisable that alcoholic drink is avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of remifentanil as in ALTIREM IV in pregnancy and lactation has not been established and is therefore not recommended (see section 4.3).

Labour and delivery

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

Breastfeeding

It is not known whether remifentanil, as in ALTIREM IV, is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanil-related material was found in rat milk after dosing with remifentanil, nursing mothers should be advised to discontinue breastfeeding for 24 hours following administration of ALTIREM IV.

Fertility

There is no data on fertility with ALTIREM IV.

4.7 Effects on ability to drive and use machines

Remifentanil such as ALTIREM IV has major influence on the ability to drive and use machines. The physician has to decide when these activities may be resumed.

If an early discharge is envisaged following treatment with remifentanil as in ALTIREM IV, patients should be advised not to drive or operate machinery as remifentanil as in ALTIREM IV can impair cognitive function. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

4.8 Undesirable effects

a. Summary of the safety profile

The most common undesirable effects associated with remifentanil, as contained in ALTIREM IV, are direct extensions of μ-opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of ALTIREM IV administration.

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Allergic reactions including anaphylaxis have been reported in patients receiving ALTIREM IV in conjunction with one or more anaesthetic agents
	Frequency unknown	Anaphylactic shock
Psychiatric disorders	Frequency unknown	Medicine dependence
Nervous system disorders	Frequent	Skeletal muscle rigidity
	Less frequent	Sedation (during recovery from general anaesthesia), headache
	Frequency unknown	Convulsions, serotonin syndrome
Cardiac disorders	Frequent	Bradycardia
	Less frequent	Asystole/cardiac arrest, usually preceded by bradycardia has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents
	Frequency unknown	Atrioventricular block

Vascular disorders	Frequent	Hypotension, post-operative hypertension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Acute respiratory depression, apnoea, difficulty in breathing, cough Hypoxia
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting Constipation, abdominal pain*, pancreatitis*
Skin and subcutaneous tissue disorders	Frequent	Pruritus
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Post-operative shivering Post-operative aches Medicine tolerance
Investigations	Frequent Less frequent	Weight gain, elevations in serum transaminases (ALT (alanine transaminase), AST (aspartate aminotransferase)) Elevations in gamma-glutamyl transferase (GGT) levels, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol

*Post-marketing experience.

c. Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Overdose with remifentanil, as in ALTIREM IV, would be manifested by an extension of the pharmacological actions of remifentanil i.e. respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. Due to the very short duration of action of remifentanil, as in ALTIREM IV, the potential for deleterious effects due to overdose are limited to the immediate time period following administration. Response to discontinuation is rapid with return to baseline within ten minutes.

Management of overdose

In the event of suspected overdosage, the following actions are to be taken:

- discontinue administration of ALTIREM IV
- maintain the patients' airway
- initiate assisted or controlled ventilation with oxygen
- maintain adequate cardiovascular function.

If depressed respiration is associated with muscle rigidity, a neuromuscular blocking medicine may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor medicines for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of an opioid antagonist such as naloxone may be given to manage severe respiratory depression and muscle rigidity. The duration of respiratory depression following overdose with remifentanil as in ALTIREM IV is unlikely to exceed the duration of action of the opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics

ATC code: N01AH06

Pharmacological classification: A 2.9 Other analgesics

Mechanism of action

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

Other pharmacological effects

Assays of histamine in patients and healthy volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 μg/kg.

Paediatric population

Neonates/infants (aged less than 1 year)

In a randomised (ratio of 2:1, remifentanil:halothane), open label, parallel group, multicentre study 60 young infants and neonates ≤ 8 weeks of age (mean 5,5 weeks) with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0,4 μg/kg/min initial continuous infusion plus supplemental doses or infusion rates changes as needed) was

compared with halothane (given at 0,4 % with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 60 % nitrous oxide (N_2O) plus 40 % oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant). Use for total intravenous anaesthesia (TIVA) - children aged 6 months to 16 years TIVA with remifentanil in paediatric surgery was compared to inhalation anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical Intervention	**Age (y), (N)**	**Study Condition (maintenance)**	**Extubation (min) (mean (SD))**
Lower abdominal/ urological surgery	0,5 - 16 (120)	TIVA: propofol (5 - 10 mg/kg/h) + remifentanil (0,125 µg/kg/min)	11,8 (4,2)
		Inhalational anaesthesia: sevoflurane (1,0 - 1,5 MAC) + remifentanil (0,125 - 1,0 µg/kg/min)	15,0 (5,6) ($p < 0,05$)
ENT-surgery	4 - 11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0,5 µg/kg/min)	11 (3,7)
		Inhalational anaesthesia:	9,4 (2,9) not significant

		desflurane (1,3 MAC) + N_2O mixture	
General or ENT surgery	2 - 12 (153)	TIVA: propofol (100 - 200 µg/kg/min) + remifentanil (0,2 - 0,5 µg/kg/min) Inhalational anaesthesia: sevoflurane (1,0 - 1,5 MAC) + N_2O mixture	Comparable extubation times (based on limited data)

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

5.2 Pharmacokinetic properties

Absorption

Since remifentanil is administered intravenously, its bioavailability is 100 %.

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3 - 10 minutes. The average clearance of remifentanil in young healthy adults is 40 mL/min/kg. Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0,1 µg/kg/min increase infusion rate, the blood concentration of remifentanil will rise 2,5 ng/mL.

Distribution

Remifentanil is approximately 70 % bound to plasma proteins.

In a human clinical trial, the average maternal remifentanil concentrations were approximately twice those seen in the foetus. In some cases, however, foetal concentrations were similar to those in the mother. The umbilical arteriovenous ratio of remifentanil concentrations was approximately 30 % suggesting metabolism of remifentanil in the neonate. Remifentanil related material is transferred to the milk of lactating rats.

Biotransformation

Remifentanil is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. Studies in man indicate that all pharmacological activity is associated with the parent compound. The activity of this metabolite is therefore not of any clinical consequence.

The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite (1/4600th as potent as remifentanil).

The half-life of the metabolite in healthy adults is 2 hours. Approximately 95 % of remifentanil is recovered in the urine as the carboxylic acid metabolite.

Remifentanil is not a substrate for plasma cholinesterase.

Elimination

Approximately 95 % of remifentanil in the form of the carboxylic acid metabolite is recovered in the urine in patients with normal renal function.

The central volume of distribution is 100 mL/kg, and the steady-state volume of distribution is 350 mL/kg. In children aged 1 - 12 years, remifentanil clearance and volume of distribution decreases with increasing age; the values of these parameters in neonates are approximately twice those of healthy young adults.

Placental and milk transfer

Remifentanil crosses the placenta and appears in breast milk. In studies, the mean ratio of maternal

arterial to umbilical venous concentration indicated that the neonate was exposed approximately 50 % concentration of remifentanil to that in the mother. The mean umbilical arteriovenous ratio of remifentanil concentrations was approximately 30 % suggesting metabolism of remifentanil in the neonate.

Cardiac anaesthesia

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

Pharmacokinetics in special patient groups

Renal impairment

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

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment, the concentration of the carboxylic acid metabolite is expected to reach approximately 100-fold the level of remifentanil at steady state. Clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant μ-opioid receptor effects even after administration of remifentanil infusions for up to 3 days in these patients.

There is no evidence that remifentanil is extracted during renal replacement therapy. The carboxylic acid metabolite is extracted during haemodialysis by at least 30 %.

In patients with anuria the half-life of the carboxylic acid metabolite is increased to 30 hours.

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.

Patients with severe hepatic impairment may be more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored, and the dose of remifentanil should be

titrated to the individual patient need.

Elderly

The clearance of remifentanil is slightly reduced (approximately 25 %) in elderly patients (> 65 years) compared to young patients. The pharmacodynamic activity of remifentanil increases with increasing age.

Elderly patients have a remifentanil EC^{50} for the formation of delta waves on the electroencephalogram (EEG) that is 50 % lower than for 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.

Paediatric population

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 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.

5.3 Preclinical safety data

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

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

concentration of 0,1 µM. The major metabolite remifentanil acid had no effect on APD up to the maximum tested concentration of 10 µM.

Reproductive toxicity studies

Remifentanil has been shown to reduce fertility in male rats when administered daily by intravenous injection for at least 70 days at a dose of 0,5 mg/kg, or approximately 250 times the maximum recommended human bolus dose of 2 micrograms/kg.

The fertility of female rats was not affected at doses up to 1 mg/kg when administered for at least 15 days prior to mating. No teratogenic effects have been observed with remifentanil at doses up to 5 mg/kg in rats and 0,8 mg/kg in rabbits. Administration of remifentanil to rats throughout late gestation and lactation at doses up to 5 mg/kg IV had no significant effect on the survival, development, or reproductive performance of the F1 (first filial) generation.

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

ALTIREM IV should only be reconstituted and diluted with those infusion solutions recommended (see section 6.6).

ALTIREM IV should not be reconstituted, diluted or mixed with lactated Ringer's injection or lactated

Ringer's and 5 % dextrose injection, although it has shown to be compatible with these IV fluids when administered into a running IV catheter.

ALTIREM IV should not be mixed with propofol in the same infusion bag prior to administration.

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

ALTIREM IV should not be mixed with other therapeutic medicine prior to administration.

6.3 Shelf life

ALTIREM IV 1 mg: 18 months

ALTIREM IV 2 mg: 24 months

ALTIREM IV 5 mg: 36 months

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 ºC.

Do not freeze. Keep the vial in the carton until required for use.

For storage conditions of the reconstituted / diluted medicinal product, see section 6.3.

ALTIREM IV does not contain an antimicrobial preservative and thus care must be taken to assure the

sterility of prepared solutions, reconstituted product should be used promptly, and any unused material discarded.

6.5 Nature and contents of container

ALTIREM IV 1 mg is available in a clear, colourless glass (Type I), 3 mL vial, closed with a grey bromobutyl stopper and sealed with an aluminium cap having a light blue plastic flip-off cover. Pack size of 5 and 10 vials, packed in carton boxes.

ALTIREM IV 2 mg is available in a clear, colourless glass (Type I), 5 mL vial, closed with a grey bromobutyl stopper and sealed with an aluminium cap having a blue plastic flip-off cover. Pack size of 5 and 10 vials, packed in carton boxes.

ALTIREM IV 5 mg is available in a clear, colourless glass (Type I), 10 mL vial, closed with a grey bromobutyl stopper and sealed with an aluminium cap having a dark blue plastic flip-off cover. Pack size of 5 and 10 vials, packed in carton boxes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

ALTIREM IV should be prepared for intravenous use by adding, as appropriate 1, 2, or 5 mL of diluent (refer below to the list of IV fluids) to give a reconstituted solution with a concentration of 1 mg/mL remifentanil. The reconstituted solution is clear, colourless, and practically free from particulate material. After reconstitution, visually inspect the product (where the container permits) for particulate material, discolouration or damage of container. Discard any solution where such defects are observed. Reconstituted product is for single use only. Any unused material should be discarded.

The reconstituted solution is stable for 24 hours at room temperature (25 ºC) and further dilution to 20 - 250 µg/mL (50 µg/mL is the recommended dilution for adults and 20 - 25 µg/mL for paediatric

patients aged 1 year and over) with one of the following IV fluids below:

- 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.

After dilution, visually inspect the product to ensure it is clear, colourless, practically free from particulate matter and the container is undamaged. Discard any solution where such defects are observed.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

ALTIREM IV 1 mg: A52/2.9/0454

ALTIREM IV 2 mg: A52/2.9/0455

ALTIREM IV 5 mg: A52/2.9/0456

9. DATE OF FIRST AUTHORISATION

22 February 2022

10. DATE OF REVISION OF THE TEXT

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