1.5.5.1 Proposed Professional Information -clean

SCHEDULING STATUS: S6

PROPRIETARY NAMES AND DOSAGE FORM:

REMIFENTANIL 1 mg VIATRIS (powder for concentrate for solution for injection for infusion)

REMIFENTANIL 2 mg VIATRIS (powder for concentrate for solution for injection for infusion)

REMIFENTANIL 5 mg VIATRIS (powder for concentrate for solution for injection for infusion)

COMPOSITION:

Each **REMIFENTANIL 1 mg VIATRIS** vial contains 1 mg remifentanil base (as hydrochloride)

Each **REMIFENTANIL 2 mg VIATRIS** vial contains 2 mg remifentanil base (as hydrochloride)

Each **REMIFENTANIL 5 mg VIATRIS** vial contains 5 mg remifentanil base (as hydrochloride)

The other ingredients are: glycine and hydrochloric acid (for pH adjustment).

PHARMACOLOGICAL CLASSIFICATION:

A 2.9 Other analgesics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

Pharmacokinetic properties:

After administration of the recommended doses of remifentanil, the effective biological half-life is 3 to 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 in infusion rate, the blood concentration of remifentanil will rise 2,5 ng/ml. Remifentanil is approximately 70 % bound to plasma proteins.

Metabolism:

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 half-life of the metabolite in healthy adults is 2 hours. In patients with normal renal function, the time for 95 % elimination of the primary metabolite of remifentanil by the kidneys is approximately 7 to 10 hours. Remifentanil is not a substrate for plasma cholinesterase.

Approximately 95 % of remifentanil is recovered in the urine as the carboxylic acid metabolite.

Placental and milk transfers:

Remifentanil crosses the placenta and appears in breast milk.

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.

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 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 %.

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.

Paediatric patients:

In paediatric patients 5 days to 17 years of age, the average clearance and steady state volume of distribution of remifentanil are increased in younger children and decline to young healthy adult values by age 17. The half-life of remifentanil is not significantly different in neonates, suggesting that changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to that seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 - 17 years of age are similar to those seen in adults after correcting for differences in body weight.

Elderly: The clearance of remifentanil is reduced (approximately 25 %) in elderly patients (> 65 years) compared to young patients.

INDICATIONS:

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

REMIFENTANIL VIATRIS 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.

CONTRA-INDICATIONS:

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

REMIFENTANIL VIATRIS is contra-indicated in patients hypersensitive to remifentanil, to other fentanyl analogues or to any of the ingredients in **REMIFENTANIL VIATRIS**.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

REMIFENTANIL VIATRIS should not be used with nitrous oxide and oxygen alone at altitudes above sea level.

REMIFENTANIL VIATRIS should not be used unless artificial ventilation is planned.

WARNINGS AND SPECIAL PRECAUTIONS:

REMIFENTANIL VIATRIS is not for use as the sole medicine in general anaesthesia.

REMIFENTANIL VIATRIS should be administered 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.

Discontinuation of treatment

The pharmacodynamic activity of remifentanil increases with increasing age. Elderly patients have a remifentanil EC_{50} for the formation of delta waves on the 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.

Inadvertent administration:

A sufficient amount of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS** into a fast-flowing line or via a dedicated IV line, which is adequately cleared of residual medicine or which is removed upon discontinuation of **REMIFENTANIL VIATRIS.**

Dependency:

REMIFENTANIL VIATRIS may produce dependency.

Rapid offset of action:

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

Muscle rigidity – prevention and management:

At the doses 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 VIATRIS** must be treated in the context of the patient's clinical condition with appropriate supporting measures. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking medicine and/or additional hypnotic medicines. Muscle rigidity seen during the use of **REMIFENTANIL VIATRIS** as an analgesic may be treated by stopping or decreasing the rate of administration of **REMIFENTANIL VIATRIS**.

Resolution of muscle rigidity after discontinuing the infusion of **REMIFENTANIL VIATRIS** occurs within minutes.

The effects of muscle rigidity on respiration may be more pronounced in patients with myasthenia gravis.

Respiratory depression – management:

Analgesia is accompanied by marked respiratory depression. Therefore, **REMIFENTANIL VIATRIS** 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 severe hepatic impairment are more sensitive to the respiratory depressant effects.

Cardiovascular effects:

Hypotension and bradycardia may be managed by reducing the rate of infusion of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS**).

Effect on ability to drive and use of machines: If a patient will be discharged soon after treatment with anaesthetic medicines, such as **REMIFENTANIL VIATRIS**, they should be advised not to drive or operate machinery. Patients should be advised not to drive or sign any legally binding documents within 24 hours of receiving **REMIFENTANIL VIATRIS**.

Athletes:

Athletes should be warned that **REMIFENTANIL VIATRIS** contains an active substance that could give a positive result in world anti-doping tests.

INTERACTIONS:

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

The opioid, remifentanil (**REMIFENTANIL VIATRIS**), whether given by manually-controlled infusion or target controlled infusion (TCI), decreases the doses of inhaled and intravenous (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.

The cardiovascular effects of **REMIFENTANIL VIATRIS** may be exacerbated in patients receiving concomitant cardiac depressant medicines, such as beta-blockers and calcium channel blocking medicines.

PREGNANCY AND LACTATION:

REMIFENTANIL VIATRIS should not be used during pregnancy and lactation.

Safety and efficacy in pregnancy and lactation has not been established (see **CONTRA-INDICATIONS**).

Labour and delivery: The safety profile of **REMIFENTANIL VIATRIS** during labour or delivery has not been demonstrated. There are insufficient data to recommend **REMIFENTANIL VIATRIS** for use during labour and caesarean section. Remifentanil crosses the placental barrier and can cause respiratory depression in the baby.

DOSAGE AND DIRECTIONS FOR USE:

Continuous infusion of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS** after use (see **WARNINGS AND SPECIAL PRECAUTIONS**).

REMIFENTANIL VIATRIS is for intravenous use only and must not be administered by epidural or intrathecal injection (see **CONTRA-INDICATIONS**).

REMIFENTANIL VIATRIS should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5 % Dextrose Injection, but it has shown to be compatible with these IV fluids when administered into a running IV catheter.

REMIFENTANIL VIATRIS should not be mixed with propofol in the same intravenous admixture solution.

REMIFENTANIL VIATRIS should not be administered into the same intravenous line with blood/serum/plasma, as non-specific esterases in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

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

GENERAL ANAESTHESIA:

The administration of **REMIFENTANIL VIATRIS** must be individualised based on the patient's response.

Adults:

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

Dosage Guidelines for Adults:

Indication	**Bolus infusion of REMIFENTANIL VIATRIS (µg/kg)**	**Continuous infusion of REMIFENTANIL VIATRIS (µg/kg/min)**	
		Starting Rate	Range
With induction of anaesthesia in ventilated patients	1 (given over not less than 30 seconds)	0,5 to 1,0	-
Maintenance of anaesthesia in ventilated patients – isoflurane (starting dose 0,5 MAC)	0,5 to 1,0	0,25	0,05 to 0,5
- propofol (starting dose 100 µg/kg/min)	0,5 to 1,0	0,25	0,05 – 0,5

At the doses recommended, remifentanil significantly reduces the amount of hypnotic medicine required to maintain anaesthesia. Therefore, isoflurane should be administered as recommended above to avoid excessive depth of anaesthesia (see **INTERACTIONS**).

Induction of anaesthesia:

REMIFENTANIL VIATRIS should be administered with a hypnotic medicine, such as isoflurane, for the induction of anaesthesia. **REMIFENTANIL VIATRIS** can 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 to 10 minutes after the start of the **REMIFENTANIL VIATRIS**, then a bolus infusion is not necessary.

Maintenance of anaesthesia:

After endotracheal intubation, the infusion rate of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS**, the rate of administration during anaesthesia can be titrated upward in 25 – 100 % increments or downward in 25 – 50 % decrements, every 2 to 5 minutes to attain the desired level of µ-opioid response.

In response to light anaesthesia, supplemental bolus infusions may be administered every 2 to 5 minutes.

The use of **REMIFENTANIL VIATRIS** 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 VIATRIS**, residual opioid activity will be reduced within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to, or immediately following discontinuation of **REMIFENTANIL VIATRIS**. 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: REMIFENTANIL VIATRIS decreases the amounts of doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see **INTERACTIONS**).

Paediatric patients (1 – 12 years of age): Induction of anaesthesia: REMIFENTANIL VIATRIS is not recommended for the induction of anaesthesia, as insufficient data are available.

Table 1: Dosing guidelines for maintenance of anaesthesia in paediatric patients (1 – 12 years of age)

Concomitant anaesthetic medicines	**Bolus infusion of REMIFENTANIL VIATRIS (µg/kg)**	**Continuous infusion of REMIFENTANIL VIATRIS (µg/kg/min)**	
		Starting Rate	Typical Maintenance Rates

Halothane (starting dose 0,3 MAC)	1	0,25	0,05 to 1,3
Sevoflurane (starting dose 0,3 MAC)	1	0,25	0,05 to 0,9
Isoflurane (starting dose 0,5 MAC)	1	0,25	0,06 to 0,9

When given by bolus injection, **REMIFENTANIL VIATRIS** should be administered over not less than 30 seconds.

Surgery should not commence until at least 5 minutes after the start of the **REMIFENTANIL VIATRIS** 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, halogenated anaesthetics 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 VIATRIS**.

Guidelines for discontinuation: Following discontinuation of the infusion, the offset of analgesic effect of **REMIFENTANIL VIATRIS** 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 REMIFENTANIL VIATRIS (μg/kg)**	**Continuous infusion of REMIFENTANIL VIATRIS (μg/kg/min)**	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	-
Maintenance of anaesthesia - Isoflurane (starting dose 0,4 MAC) - Propofol (starting dose 50 μg/kg/min)	0,5 to 1 0,5 to 1	1 1	0,003 to 4 0,01 to 4,3

Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, **REMIFENTANIL VIATRIS** should be administered at an initial infusion rate of 1 μg/kg/min. The use of bolus infusions of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS** should be titrated according to patient need. Supplemental bolus doses may also be given as required. High risk cardiac patients, such as those with poor ventricular function, should be administered a maximum bolus dose of 0,5 μg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see **Pharmacokinetic properties: Cardiac anaesthesia**).

Concomitant medication: At doses recommended above, **REMIFENTANIL VIATRIS** significantly reduces the amount of hypnotic medicine required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane and propofol should be administered as recommended in the table above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with **REMIFENTANIL VIATRIS**.

Continuation of post-operative analgesia prior to extubation: It is recommended that the infusion of **REMIFENTANIL VIATRIS** should be maintained at the final intra-operative rate during transfer of patients to the post-operative care area. Upon arrival into this area, the 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 **REMIFENTANIL VIATRIS**, 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 **REMIFENTANIL VIATRIS** infusion is discontinued by reducing the infusion rate in three or four steps of 50 % at 10 minute intervals. During weaning from the ventilator the **REMIFENTANIL VIATRIS** infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics. It is recommended that haemodynamic changes such as hypertension and tachycardia should be treated with alternative medicine as appropriate.

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

Use in intensive care: REMIFENTANIL VIATRIS 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 **REMIFENTANIL VIATRIS** is initiated at an infusion rate of 0,1 μg/kg/min (6 μg/kg/h) to 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 **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS** 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 REMIFENTANIL VIATRIS within the intensive care setting	
Continuous infusion μg/kg/min (μg/kg/h)	
Starting rate	**Range**
0,1(6) to 0,15(9)	0,006(0,36) to 0,74(44,4)

Bolus doses of **REMIFENTANIL VIATRIS** are not recommended in the intensive care setting.

The use of **REMIFENTANIL VIATRIS** will reduce the dosage requirement of any concomitant sedative medicines by approximately 50 %. Typical starting doses for sedative medicines, 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 medicine, sedative medicine should not be administered as an admixture.

Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the existing **REMIFENTANIL VIATRIS** infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that a **REMIFENTANIL VIATRIS** 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 to 5 minutes in increments of 25 % - 50 % in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0,25 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 REMIFENTANIL VIATRIS: Due to the very rapid offset of action of **REMIFENTANIL VIATRIS**, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Prior to discontinuation of **REMIFENTANIL VIATRIS**, 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 **REMIFENTANIL VIATRIS**.

Guidelines for extubation and discontinuation of REMIFENTANIL VIATRIS: In order to ensure a smooth emergence from a **REMIFENTANIL VIATRIS**-based regimen, it is recommended that the infusion rate of **REMIFENTANIL VIATRIS** 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 **REMIFENTANIL VIATRIS** infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of **REMIFENTANIL VIATRIS**, 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 patient populations: Elderly (over 65 years of age): General anaesthesia: The initial starting dose of **REMIFENTANIL VIATRIS** 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 **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 **REMIFENTANIL VIATRIS** should be reduced and based upon ideal body weight, as the clearance and volume of distribution of remifentanil are better correlated with ideal body weight than actual body weight in this population.

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 VIATRIS**. These patients should be closely monitored and the dose of **REMIFENTANIL VIATRIS** titrated to individual patient need.

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

ASA III/IV patients: General anaesthesia: As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised in the administration of **REMIFENTANIL VIATRIS** in this population. 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 ICU: No data are available on the long-term (longer than 72 hours) use of **REMIFENTANIL VIATRIS** in ICU patients.

Reconstitution:

The reconstituted solution is stable for 24 hours at room temperature (25 °C) and further dilution to 20 to 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

SIDE-EFFECTS:

The following side-effects have been reported:

Immune system disorders:

Reported but frequency unknown: Allergic reactions including anaphylaxis.

Nervous system disorders:

Frequent: Skeletal muscle rigidity.

Less frequent: Sedation (during recovery from general anaesthesia), headache.

Cardiac disorders:

Frequent: Bradycardia.

Reported but frequency unknown: Asystole/cardiac arrest, usually preceded by bradycardia.

Vascular disorders:

Frequent: Hypotension, post-operative hypertension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Acute respiratory depression, apnoea, difficulty in breathing.

Less frequent: Hypoxia.

Gastrointestinal disorders:

Frequent: Nausea, vomiting.

Less frequent: Constipation.

Skin and subcutaneous tissue disorders:

Frequent: Pruritus.

General disorders and administration site conditions:

Frequent: Post-operative shivering.

Less frequent: Post-operative aches.

Investigations:

Frequent: Weight gain, elevations in serum transaminases (ALT, AST).

Less frequent: Elevations in gamma-GT levels, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **SIDE-EFFECTS**)

Overdose with **REMIFENTANIL VIATRIS** would be manifested by an extension of the pharmacologically predictable actions of remifentanil, e.g. respiratory depression, bradycardia, hypotension and skeletal muscle rigidity.

Due to the short duration of action of **REMIFENTANIL VIATRIS**, 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 ten minutes.

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

Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote to manage severe depression and muscle rigidity. The duration of respiratory depression following overdose with **REMIFENTANIL VIATRIS** is unlikely to exceed the duration of action of the opioid antagonist.

IDENTIFICATION:

REMIFENTANIL 1 mg/2 mg/5 mg VIATRIS:

Powder for concentrate for solution for injection or infusion.

Sterile, endotoxin-free, preservative-free, white to off-white, lyophilised powder.

The reconstituted solution is clear, colourless and practically free from particulate material.

PRESENTATION:

REMIFENTANIL 1 mg/2 mg/5 mg VIATRIS:

Vials containing 1 mg or 2 mg or 5 mg remifentanil base (as hydrochloride) available in packs of 5.

After reconstitution the solution contains 1 mg/ml, if prepared as recommended.

REMIFENTANIL 1 mg VIATRIS is packed in a Type I, colourless glass 3 ml vial with a grey, chlorobutyl stopper and flip-off cap.

REMIFENTANIL 2 mg VIATRIS is packed in a Type I, colourless glass 3 ml vial with a grey, chlorobutyl stopper and flip-off cap.

REMIFENTANIL 5 mg VIATRIS is packed in a Type I, colourless glass 6 ml vial with a grey chlorobutyl stopper and flip-off cap.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25 ºC.

Chemical and physical in-use stability of the diluted solution has been demonstrated for 4 hours at 25 ºC.

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 to 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

REMIFENTANIL 1 mg VIATRIS: 45/2.9/0658

REMIFENTANIL 2 mg VIATRIS: 45/2.9/0659

REMIFENTANIL 5 mg VIATRIS: 45/2.9/0660

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris South Africa (Pty) Ltd

4 Brewery Street,

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