1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S6

PROPRIETARY NAME AND DOSAGE FORM:

ULTIVA® 1 mg Injection

ULTIVA® 2 mg Injection

ULTIVA® 5 mg Injection

COMPOSITION:

Each ULTIVA 1 mg vial contains remifentanil hydrochloride equivalent to 1 mg remifentanil base

Each ULTIVA 2 mg vial contains remifentanil hydrochloride equivalent to 2 mg remifentanil base

Each ULTIVA 5 mg vial contains remifentanil hydrochloride equivalent to 5 mg remifentanil base

Excipients

Glycine

PHARMACOLOGICAL CLASSIFICATION:

A 2.9 Other analgesics

PHARMACOLOGICAL 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 antagonized by narcotic antagonists such as naloxone.

Pharmacokinetic properties:

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 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. 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.

Placental and milk transfer: Remifentanil crosses the placenta and appears in breast milk. In a human clinical trial, the concentration of remifentanil in foetal blood was approximately 50 % of that in maternal blood. The foetal arterio-venous ratio of remifentanil concentrations was approximately 30 % suggesting metabolism of remifentanil in the neonate.

Cardiac anaesthesia: The clearance of remifentanil is reduced by 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 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 slightly reduced (approx. 25 %) in elderly patients (>65 years) compared to young patients.

Elderly patients have a remifentanil EC_{50} for the formation of delta waves on the EEG that is 50 % lower than young patients do; therefore, the initial dose of remifentanil should be reduced by 50 % in elderly patients and then carefully titrated to meet the individual patient need.

INDICATIONS:

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

ULTIVA 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 has not been demonstrated.

CONTRA-INDICATIONS:

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

Known hypersensitivity to any component of the preparation and other fentanyl analogues.

Safety in pregnancy and lactation has not been established.

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

ULTIVA should not be used unless artificial ventilation is planned.

WARNINGS:

ULTIVA is not recommended for use as the sole agent in general anaesthesia.

ULTIVA 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.

Inadvertent administration:

A sufficient amount of ULTIVA 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 ULTIVA 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 ULTIVA.

ULTIVA may produce dependency.

INTERACTIONS:

ULTIVA is not metabolised by plasma cholinesterase and therefore interactions with medication metabolised by this enzyme are not anticipated.

ULTIVA decreases the amounts or doses of inhaled and IV 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 ULTIVA (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant medicines, such as beta-blockers and calcium channel blocking agents.

PREGNANCY AND LACTATION:

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

DOSAGE AND DIRECTIONS FOR USE:

Continuous infusion of ULTIVA 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 ULTIVA after use (see WARNINGS).
ULTIVA is for intravenous use only and must not be administered by epidural or intrathecal injection (see CONTRA-INDICATIONS).

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

ULTIVA 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.

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

ULTIVA 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.

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

GENERAL ANAESTHESIA:

The administration of ULTIVA must be individualized based on the patient's response.

Adults:

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

Dosing Guidelines for Adults

Indication	Bolus Infusion of Ultiva (µg/kg)	Continuous Infusion of Ultiva (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)	0,5-1,0	0,25	0,05-0,5
- propofol (starting dose 100 µg/kg/min)	0,5-1	0,25	0,05-0,5

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

Induction of anaesthesia: ULTIVA should be administered with a hypnotic agent, such as isoflurane, for the induction of anaesthesia. ULTIVA 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 ULTIVA infusion, then a bolus infusion is not necessary.

Maintenance of anaesthesia: After endotracheal intubation, the infusion rate of ULTIVA 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 ULTIVA, 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 ULTIVA 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 ULTIVA, 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 ULTIVA. 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: ULTIVA decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see INTERACTIONS).

Paediatric patients (1 - 12 years of age):

Induction of anaesthesia: ULTIVA 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)

CONCOMITANT ANAESTHETIC AGENT	BOLUS INFUSION OF ULTIVA (µg/kg)	CONTINUOUS INFUSION OF ULTIVA (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 infusion, ULTIVA should be administered over not less than 30 seconds.

Surgery should not commence until at least 5 minutes after the start of the ULTIVA 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, ULTIVA significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with ULTIVA.

Guidelines for discontinuation: Following discontinuation of the infusion, the offset of analgesic effect of ULTIVA 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:

Dosing Guidelines for Cardiac Anaesthesia

INDICATION	BOLUS INFUSION OF ULTIVA (µg/kg)	CONTINUOUS INFUSION OF ULTIVA (µg/kg/min)	
		Starting Rate	Typical Infusion rates
Intubation	Not recommended	1	-
Maintenance of anaesthesia			
• Isoflurane (starting dose 0,4 MAC)	0,5 to 1	1	0,003 to 4
• Propofol (starting dose 50 µg/kg/min)	0,5 to 1	1	0,01 to 4,3
Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, ULTIVA should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus infusions of ULTIVA 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 ULTIVA 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 the doses recommended above, ULTIVA significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with ULTIVA.

Continuation of post-operative analgesia prior to extubation: It is recommended that the infusion of ULTIVA 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 ULTIVA, patients must be given alternative analgesic and sedative agent 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.

It is recommended that the ULTIVA 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 ULTIVA infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

It is recommended that haemodynamic changes such as hypertension and tachycardia should be treated with alternative agents as appropriate.

Paediatric patients:

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

USE IN INTENSIVE CARE:

ULTIVA 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 ULTIVA 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 ULTIVA 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 agent is initiated (see below). The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the ULTIVA infusion rate in increments of 0,025 µg/kg/min (1,5 µg/kg/h) may be made if additional analgesia is required.

The following table summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients:

Dosing Guidelines for Use of ULTIVA 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 ULTIVA are not recommended in the intensive care setting.

The use of ULTIVA will reduce the dosage requirement of any concomitant sedative agents by approximately 50 %. Typical starting doses for sedative agents, if required, are given 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 separate titration of the respective agents, sedative agents should not be administered as an admixture.

***Additional analgesia for ventilated patients undergoing stimulating procedures*:** An increase in the existing ULTIVA 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 ULTIVA 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 ULTIVA: Due to the very rapid offset of action of ULTIVA, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Prior to discontinuation of ULTIVA, patients must be given alternative analgesic and sedative agents at a sufficient time in advance, to allow the therapeutic effects of these agents to become established. It is therefore recommended that the choice of agent(s), the dose and the time of administration, are planned prior to discontinuation of ULTIVA.

Guidelines for extubation and discontinuation of ULTIVA:

In order to ensure a smooth emergence from an ULTIVA-based regimen, it is recommended that the infusion rate of ULTIVA 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 ULTIVA infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of ULTIVA, the IV cannula should be cleared or removed to prevent subsequent inadvertent administration.

When other opioid agents 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 agents.

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 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 ULTIVA 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 remifentanil 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 ULTIVA 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 ULTIVA in ICU patients.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1 000 and <1/100), rare (≥1/10 000 and <1/1 000) and very rare (<1/10 000).

Nervous System Disorders:

Very common: skeletal muscle rigidity

Rare: sedation (during recovery from general anaesthesia)

Cardiac Disorders:

Common: bradycardia

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

These adverse events resolve within minutes of discontinuing or decreasing the rate of ULTIVA administration.

Post-marketing Data:

The following adverse events have been determined from post-marketing reporting:

Immune System Disorders: allergic reactions including anaphylaxis have been reported in patients receiving ULTIVA in conjunction with one or more anaesthetic agents.

Cardiac Disorders: cardiac arrest, asystole usually preceded by bradycardia, have been reported in patients receiving ULTIVA in conjunction with other anaesthetic agents.

Patients with severe hepatic impairment are more sensitive to the respiratory depressant effects.

Rapid offset of action:

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

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 ULTIVA must be treated in the context of the patient's clinical condition with appropriate supporting measures.

Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents.

Muscle rigidity seen during the use of ULTIVA as an analgesic may be treated by stopping or decreasing the rate of administration of ULTIVA. Resolution of muscle rigidity after discontinuing the infusion of ULTIVA occurs within minutes.

Respiratory depression – management:

Analgesia is accompanied by marked respiratory depression. Therefore, ULTIVA 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 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 may be managed by reducing the rate of infusion of ULTIVA or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolaemic and elderly patients are more sensitive to the cardiovascular effects of ULTIVA.

Pre-Clinical Safety Data:

Remifentanil produced increases in action potential duration (APD) in dog isolated Purkinje fibres. 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.

Effects on Ability to Drive and Use Machines:

If an early discharge is envisaged following treatment using anaesthetic agents, patients should be advised not to drive or operate machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and signs:

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

Treatment:

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

- discontinue administration of ULTIVA
- 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 vasopressor agents 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 ULTIVA is unlikely to exceed the duration of action of the opioid antagonist.

IDENTIFICATION:

Glass vials containing a white to off-white powder cake that may be intact or fragmented. Reconstituted solutions are clear and colourless.

PRESENTATION:

ULTIVA 1 mg: Five 3ml glass vials containing remifentanil hydrochloride (equivalent to 1mg remifentanil base) as the lyophilized powder.

ULTIVA 2 mg: Five 5ml glass vials containing remifentanil hydrochloride (equivalent to 2mg remifentanil base) as the lyophilized powder.

ULTIVA 5 mg: Five 10ml glass vials containing remifentanil hydrochloride (equivalent to 5mg remifentanil base) as the lyophilized powder.

STORAGE INSTRUCTIONS:

Keep out of reach of children.

Store at or below 25 °C.

The reconstituted solution is stable for 24 hours at 25 °C.

REGISTRATION NUMBER:

ULTIVA 1 mg: 31/2.9/0078

ULTIVA 2 mg: 31/2.9/0079

ULTIVA 5 mg: 31/2.9/0080

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

Pharmacare Limited

Healthcare Park

Woodlands Drive

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

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