DATA SHEET

1. PRODUCT NAME ULTIVA®

Remifentanil hydrochloride for injection1mg and 2mg (remifentanil base) vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance –

Remifentanil hydrochloride – 1mg and 2 mg as remifentanil base

List of Excipients -

Glycine, Hydrochloric acid, Sodium hydroxide and water for injection

3. PHARMACEUTICAL FORM

ULTIVA, for injection, is a sterile, endotoxin-free, preservative-free, white to off white, lyophilised powder, to be reconstituted before use.

When reconstituted as directed, solutions of ULTIVA are clear and colourless and contain 1mg/mL of remifentanil base as remifentanil hydrochloride.

ULTIVA for injection is available as glass vials containing 1mg or 2mg of remifentanil base.

Lyophilized powder for reconstitution for intravenous administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ULTIVA is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery. ULTIVA may also be used for continuation of analgesia into the immediate post-operative period under close supervision, during transition to longer acting analgesia.

ULTIVA is indicated for provision of analgesia and sedation in mechanically ventilated intensive care patients.

4.2 Dose and method of administration

When reconstituted as directed, solutions of ULTIVA are clear and colourless and contain 1mg/mL of remifentanil base as remifentanil hydrochloride.

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

Continuous infusions 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 (see Instructions for use/handling for additional information, including tables with examples of infusion rates by body weight to help titrate ULTIVA to the patient's anaesthetic needs).

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 and Precautions).

ULTIVA is for intravenous use only and must not be administered by epidural or intrathecal injection (see Contraindications).

ULTIVA is stable for 24 hours at room temperature (25°C) after reconstitution and further dilution with one of the following IV fluids listed 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.

(See Instructions for use/handling for additional information, including tables to help titrate ULTIVA to the patient’s anaesthetic needs).

For manually-controlled infusion remifentanil can be diluted to concentrations of 20 to 250micrograms/mL (50micrograms/mL is the recommended dilution for adults and 20 to 25micrograms/mL for paediatric patients aged 1 year and over).

GENERAL ANAESTHESIA

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

- **Adults**

The following table summarises the starting infusion rates and dose range:-

DOSING GUIDELINES FOR ADULTS

INDICATION	BOLUS INFUSION OF ULTIVA (mcg/kg)	CONTINUOUS INFUSION OF ULTIVA (mcg/kg/min)	
		Starting Rate	Range
Induction of anaesthesia in ventilated patients	1 (give over at least 30 seconds)	0.5 to 1	-
Maintenance of anaesthesia in ventilated patients			
Nitrous oxide (66%)	0.5 to 1	0.4	0.1 to 2
Isoflurane (starting dose 0.5MAC)	0.5 to 1	0.25	0.05 to 2
Propofol (Starting dose 100mcg/kg/min)	0.5 to 1	0.25	0.05 to 2
Spontaneous ventilation anaesthesia	Not recommended	0.04	0.025 to 0.1
Continuation of analgesia into the immediate post-operative period	Not recommended	0.1	0.025 to 0.2

When given by bolus infusion at induction ULTIVA should be administered over at least 30 seconds.

At the doses recommended above, ULTIVA significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia (see Dosage and Administration, General Anaesthesia, Concomitant medication). No data are available for dosage recommendations for simultaneous use of other hypnotics with ULTIVA.

Induction of anaesthesia: ULTIVA should be administered with a hypnotic agent, such as propofol, thiopentone, or isoflurane, for the induction of anaesthesia. ULTIVA can be administered at an infusion rate of 0.5 to 1mcg/kg/min with or without an initial bolus infusion of 1mcg/kg over at least 30 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes

after the start of the infusion of ULTIVA, then a bolus infusion is not necessary.

Maintenance of anaesthesia: After endotracheal intubation, the infusion rate of ULTIVA should be decreased, according to 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% to 100% increments or downward in 25% to 50% decrements, every 2 to 5 minutes to attain the desired level of mu-opioid response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 to 5 minutes.

Anaesthesia in spontaneously breathing anaesthatised patients with a secured airway (eg laryngeal mask anaesthesia): In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended starting infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04mcg/kg/min with titration to effect. A range of infusion rates from 0.025 to 0.1mcg/kg/min has been studied. Bolus injections are not recommended in spontaneously breathing anaesthetised patients.

Continuation into the immediate post-operative period: In the event that longer acting analgesia has not been established prior to the end of surgery, ULTIVA may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.

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

In patients who are breathing spontaneously, the infusion rate of ULTIVA should initially be decreased to a rate of 0.1mcg/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025mcg/kg/min every five minutes, to balance the patient's level of analgesia and respiratory rate. ULTIVA should only be used in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, under the close supervision of persons specifically trained in the recognition and management of the respiratory effects of potent opioids.

The use of bolus injections of 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 no residual opioid activity will be present 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).

Doses of the following agents used in anaesthesia, isoflurane, thiopentone, propofol and temazepam have been reduced by up to 75% when used concurrently with ULTIVA.

- **Paediatric patients (1-12 years of age):**

Induction of anaesthesia: There are insufficient data to make a dosage recommendation.

Maintenance of anaesthesia:

DOSING GUIDELINES FOR MAINTENANCE OF ANAESTHESIA IN PAEDIATRIC PATIENTS (1-12 years of age)

CONCOMITANT ANAESTHETIC AGENT	BOLUS INFUSION OF ULTIVA (mcg/kg)	CONTINUOUS INFUSION OF ULTIVA (mcg/kg/min)	
		Starting Rate	**Typical Maintenance Rates**
Nitrous oxide (70%)	1	0.4	0.4 to 3
Halothane (starting dose 0.3MAC)	1	0.25	0.05 to 1.3
Sevoflurane (starting dose 0.3MAC)	1	0.25	0.05 to 0.9
Isoflurane (starting dose 0.5MAC)	1	0.25	0.06 to 0.9

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

When given by bolus infusion, ULTIVA should be administered over at least 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 (see Dosage and Administration, Adults - Concomitant medication).

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 Dosage and Administration, 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 for 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 (mcg/kg)	CONTINUOUS INFUSION OF ULTIVA (mcg/kg/min)	
		Starting Rate	**Typical Infusion Rates**
Intubation	Not recommended	1	_
Maintenance of anaesthesia			
• Isoflurane (starting dose 0.4MAC)	0.5 to 1	1	0.003 to 4
• Propofol (starting dose 50mcg/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 1mcg/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 0.5mcg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see Uses, Pharmacokinetics, Characteristics in Patients - Cardiac anaesthesia).

Concomitant medication: At the doses recommended above, ULTIVA significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with ULTIVA (see Dosage and Administration, Adults - Concomitant medication).

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 patient's level of analgesia and sedation should be closely monitored and the ULTIVA infusion rate adjusted to meet the individual patient's requirements.

Guidelines for discontinuation: Prior to discontinuation of ULTIVA, patients must be given alternative analgesic and sedative agents at a sufficient time in advance. The choice and dose of agent(s) should be appropriate for the patient's level of post-operative care (See Dosage and Administration, Adults - Guidelines for discontinuation).

It is recommended that the ULTIVA infusion is discontinued by reducing the infusion rate 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.

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

- **Adults**

ULTIVA can be initially used alone for the provision of analgesia and sedation in mechanically ventilated intensive care patients.

It is recommended that ULTIVA is initiated at an infusion rate of 0.1mcg/kg/min to 0.15mcg/kg/min. The infusion rate should be titrated in increments of 0.025mcg/kg/min to achieve the desired level of analgesia and sedation. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the ULTIVA infusion rate adjusted accordingly. If an infusion rate of 0.2mcg/kg/min is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent is initiated. 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 0.025mcg/kg/min may be made if additional analgesia is required.

The safety and efficacy of ULTIVA in mechanically ventilated intensive care patients has been established from well-controlled clinical trials for infusions of up to 3 days. Therefore the use of ULTIVA is not recommended for a duration of treatment greater than 3 days.

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 micrograms/kg/min	
Starting Rate	**Range**
0.1 to 0.15	0.006 to 0.74

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. Typical starting doses for sedative agents, if required, are given below.

RECOMMENDED STARTING DOSE OF SEDATIVE AGENTS, IF REQUIRED:

Sedative Agents	**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 prepared as one mixture in the same infusion bag.

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 0.1mcg/kg/min should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25%-50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25micrograms/kg/min, maximum 0.75micrograms/kg/min, has been administered for provision of additional anaesthesia during stimulating procedures.

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

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 0.1mcg/kg/min 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.

- **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.

Populations

- **Elderly (over 65 years of age):**

General Anaesthesia: The initial starting dose of ULTIVA administered to patients over 65 should be half the recommended adult dose and then titrated to individual patient need as an increased sensitivity to the pharmacological effects of ULTIVA 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 Dosage and Administration, Cardiac Anaesthesia – Dosing guidelines).

Intensive Care: No initial dose reduction is required (see Dosage and Administration, Use in Intensive Care).

- **Obese patients:**

It is recommended that for obese patients the dosage of ULTIVA should be reduced and based upon ideal body weight as the clearance and volume of distribution of ULTIVA are better correlated with ideal body weight than actual body weight in this population.

- **Renal impairment:**

No dosage adjustment, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of ULTIVA is unchanged in this patient population.

- **Hepatic impairment:**

No adjustment of the initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of ULTIVA is unchanged in this patient population. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of ULTIVA. These patients should be closely monitored and the dose of ULTIVA 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 Dosage and Administration, Cardiac Anaesthesia- Dosing guidelines).

4.3 Contraindications

As glycine is present in the formulation ULTIVA is contraindicated for epidural and intrathecal use (see Warnings and Precautions, Other, Preclinical Safety Data).

ULTIVA is contraindicated in patients with known hypersensitivity to any component of the preparation and other fentanyl analogues.

4.4 Special warnings and precautions for use

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

As with all opioids, ULTIVA is not recommended for use as the sole agent in general anaesthesia.

Patients with a known hypersensitivity to opioids of a different class may exhibit a hypersensitivity reaction following administration of Ultiva. Caution should be exercised before using Ultiva in these patients (see **Contraindications**).

Muscle rigidity - prevention and management: At the doses recommended muscle rigidity may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, bolus infusions should be administered over at least 30 seconds.

Muscle rigidity induced by ULTIVA must be treated in the context of the patients 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.

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

Respiratory depression - management: As with all potent opioids, profound 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 temporary discontinuation of the infusion. Unlike other fentanyl analogues ULTIVA has not been shown to cause recurrent respiratory depression even after prolonged administration. However, as many factors may affect post-operative recovery it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

Cardiovascular effects: Hypotension and bradycardia (see Adverse Effects) may be managed by 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 may be more sensitive to the cardiovascular effects of ULTIVA.

Rapid offset of action: Due to the very rapid offset of action of ULTIVA, no residual opioid activity will be present within 5-10 minutes after the 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.

Discontinuation of Treatment: Symptoms including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of remifentanil. Where reported, re-introduction and tapering of the infusion has been beneficial.

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.

Drug abuse: As with other opioids ULTIVA may produce dependency.

4.5 Interaction with other medicines and other forms of interaction

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

As with other opioids remifentanil decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see Dosage and Administration, Adults - Concomitant medication). 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.

4.6 Fertility, pregnancy and lactation

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

ULTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation: It is not known whether remifentanil 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, caution should be exercised when ULTIVA is administered to a nursing mother.

Labour and Delivery: 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.

ULTIVA crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

4.7 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.

4.8 Undesirable effects

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

Clinical Trial Data

The most common adverse events associated with ULTIVA are direct extensions of mu-opioid agonist pharmacology. The overall reporting incidence, as determined from all phases of controlled anaesthesia studies at recommended doses, is presented below. These adverse events resolve within minutes of discontinuing or decreasing the rate of ULTIVA administration.

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

Postmarketing Data

The following adverse events and reporting frequencies have been determined from postmarketing reporting:

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

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

4.9 Overdose

As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil.

Due to the very short duration of action of ULTIVA, 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 ULTIVA, 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 agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacological properties

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

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

5.2 Pharmacokinetics properties

Absorption: Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1micrograms/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5nanograms/mL.

Distribution: The central volume of distribution is 100mL/kg, and the steady-state volume of distribution is 350mL/kg.

Remifentanil is approximately 70% bound to plasma proteins.

Biotransformation: 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.

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

Characteristics in Patients:

Cardiac Anaesthesia: The clearance of remifentanil is reduced by up to 20% during hypothermic (28^{o}C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree Centigrade.

Renal impairment: The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status.

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

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. In intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite may exceed 250-fold the level of remifentanil at steady-state in some patients. Clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant mu-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 slightly 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 (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 EC50 for formation of delta waves on the electroencephalogram (EEG) that is 50% lower than young patients; therefore, the initial dose of remifentanil should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

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

5.3 Preclinical safety data

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 ULTIVA.

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 1μM or higher (which are higher than plasma concentrations seen in clinical practice). There were no effects at a concentration of 0.1μM.

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

Remifentanil-related material was found in rat milk after dosing with remifentanil. Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanil and/or its metabolites during growth and development.

There have been no additional findings of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, Hydrochloric acid, Sodium hydroxide and water for injection

6.2 Incompatibilities

ULTIVA should only be reconstituted and diluted with those infusion solutions recommended (see Instructions for Use/Handling).

It should not be reconstituted, diluted or mixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Dextrose Injection.

ULTIVA should not be mixed with propofol in the same intravenous infusion bag prior to administration.

Administration of ULTIVA into the same intravenous line with blood/serum/plasma is not recommended. Non-specific esterase 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.

6.3 Shelf life

1mg vials - 18 months.

2mg vials - Two years.

6.4 Special precautions for storage

Store at or below 25°C.

The reconstituted solution of ULTIVA is chemically and physically stable for 24 hours at room temperature (25°C). However, ULTIVA 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

1mg Remifentanil lyophilised powder in 3mL glass vials in cartons of 5.

2mg Remifentanil lyophilised powder in 5mL glass vials in cartons of 5.

6.6 Special precautions for handling and disposal

Instructions for Use/Handling

ULTIVA is stable for 24 hours at room temperature (25°C) after reconstitution and further dilution to 20 to 250mcg/mL (50mcg/mL is the recommended dilution for adults and 20-25mcg/mL for paediatric patients aged 1 year and over) with one of the following IV fluids listed 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 has been shown to be compatible with the following intravenous fluids when administered into a running IV infusion of:-

- Lactated Ringer's Injection.
- Lactated Ringer's and 5% Dextrose Injection

ULTIVA has been shown to be compatible with propofol when administered into a running IV infusion. The following tables give guidelines for infusion rates of ULTIVA:-

Table 1: ULTIVA for Injection Infusion Rates (mL/kg/h)

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate (mL/kg/h) for Solution Concentrations of			
	20mcg/mL 1mg/50mL	25mcg/mL 1mg/40mL	50mcg/mL 1mg/20mL	250mcg/mL 10mg/40mL
0.0125	0.038	0.03	0.015	not recommended
0.025	0.075	0.06	0.03	not recommended
0.05	0.15	0.12	0.06	0.012
0.075	0.23	0.18	0.09	0.018
0.1	0.3	0.24	0.12	0.024
0.15	0.45	0.36	0.18	0.036
0.2	0.6	0.48	0.24	0.048
0.25	0.75	0.6	0.3	0.06
0.5	1.5	1.2	0.6	0.12
0.75	2.25	1.8	0.9	0.18
1.0	3.0	2.4	1.2	0.24
1.25	3.75	3.0	1.5	0.3
1.5	4.5	3.6	1.8	0.36
1.75	5.25	4.2	2.1	0.42
2.0	6.0	4.8	2.4	0.48

Table 2: ULTIVA for Injection Infusion Rates (mL/h) for a 20mcg/mL Solution

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

0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 3: ULTIVA for Injection Infusion Rates (mL/h) for a 25mcg/mL Solution

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

Table 4: ULTIVA for Injection Infusion Rates (mL/h) for a 50mcg/mL Solution

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

Table 5: ULTIVA for Injection Infusion Rates (mL/h) for a 250mcg/mL Solution

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

7. MEDICINE SCHEDULE

Controlled Drug, Class B3

8. SPONSOR

Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
58 Richard Pearce Drive
Airport Oaks
Auckland, New Zealand

Ph (09) 918 5100 Fax (09) 901 5101

9. DATE OF FIRST APPROVAL

16 Jan 1997

10. DATE OF REVISION OF THE TEXT

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SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
Sponsor details Format	Change from sponsorship of Glaxo to Pharmacy Retailing Format revised in accordance with new Medsafe template