ULTIVA

Remifentanil hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Remifentanil for injection is a sterile, preservative-free, white to off white, lyophilised powder, to be reconstituted before use. When reconstituted as directed, solutions of remifentanil for injection are clear and colourless and contain 1 mg/ml of remifentanil base as remifentanil hydrochloride.

Excipient(s) with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'. (*See List of Excipients*")

PHARMACEUTICAL FORM

Sterile, endotoxin-free non-pyrogenic, preservative-free, white to off white, lyophilised

CLINICAL PARTICULARS

Indications

ULTIVA is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery, and also 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.

Dosage and Administration

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 drugs 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 i.v. line or via a dedicated i.v. 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 i.v. use only and must not be administered by epidural or intrathecal injection (*see Contraindications*).

ULTIVA for injection is stable for 24 hours at room temperature (25°C) after reconstitution and further dilution to 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml for paediatric patients aged 1 year and over) with one of the following i.v. 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).

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

GENERAL ANAESTHESIA

- **Adults**

The following table summarises the starting infusion rates and dose range.

DOSING GUIDELINES FOR ADULTS

INDICATION	BOLUS INFUSION OF REMIFENTANIL (micrograms/kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/kg/min)	
		Starting Rate	Range
Induction of anaesthesia in ventilated patients	1 (give over not less than 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 100 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2
Anaesthesia in spontaneously breathing anaethetised patients with secured airway	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 not less than 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 Concomitant medication* in this section). 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 1 micrograms/kg/min with or without an initial bolus infusion of 1 microgram/kg over not less than 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 remifentanil, 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 anaesthetised patients with a secured airway (e.g. laryngeal mask anaesthesia)

In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended starting

infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04 micrograms/kg/min with titration to effect. A range of infusion rates from 0.025 to 0.1 micrograms/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 0.1 micrograms/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025 micrograms/kg/min every 5 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.

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*.

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.

The patient may experience symptoms including tachycardia, tachypnea, hypertension and agitation, on discontinuation of treatment with remifentanil (*see Warnings and Precautions, Discontinuation of Treatment*).

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

CONCOMITANT ANAESTHETIC AGENT	BOLUS INFUSION OF REMIFENTANIL (micrograms/ kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/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

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* (*see Dosage and Administration - General Anaesthesia - 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 - General Anaesthesia – Adults - Guidelines for discontinuation*).

- **Neonates/infants (aged less than 1 year)**

The pharmacokinetic profile of *ULTIVA* 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 REMIFENTANIL (micrograms/kg)	CONTINUOUS INFUSION OF REMIFENTANIL (micrograms/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 50 micrograms/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 microgram/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 micrograms/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (*see Pharmacokinetics*).

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 - General Anaesthesia - 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 - General Anaesthesia - 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 minutes 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

ULTIVA TCI (Target Controlled Infusion) has not been studied in intensive care patients.

- **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 0.1 micrograms/kg/min to 0.15 micrograms/kg/min. The infusion rate should be titrated in increments of 0.025 micrograms/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 0.2 micrograms/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 0.025 micrograms/kg/min may be made if additional analgesia is required.

ULTIVA has been studied in intensive care patients in well controlled clinical trials for up to 3 days. There are limited additional clinical trial data for longer durations.

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 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 0.1 micrograms/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% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min, maximum 0.75 micrograms/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 a remifentanil-based regimen it is recommended that the infusion rate of *ULTIVA* is titrated in stages to 0.1 micrograms/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 minutes 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.

The patient may experience symptoms including tachycardia, tachypnea, hypertension and agitation, on discontinuation of treatment with remifentanil (*see Warnings and Precautions, Discontinuation of Treatment*).

- **Paediatric intensive care patients**

There are no data available on use in paediatric patients.

Other 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 remifentanil 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 in renally impaired patients, including those undergoing renal replacement therapy, 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 remifentanil. 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*).

Contraindications

As glycine is present in the formulation *ULTIVA* is contraindicated for epidural and intrathecal use (*see Pre-Clinical Safety Data*).

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

Warnings and Precautions

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 drugs 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 remifentanil in these patients (*see Contraindications*).

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Ultiva and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Ultiva concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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 not less than 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 Reactions*) may be managed by reducing the rate of infusion of *ULTIVA* or the dose of concurrent anaesthetics or by using i.v. fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolaemic, and elderly patients may be more sensitive to the cardiovascular effects of *ULTIVA*.

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 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, tachypnea, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration (in the reports, patients had received from between 2 to 33 days) of remifentanil. The time to onset of symptoms ranged from minutes to four hours. Where reported, re-introduction and tapering of the remifentanil infusion or administration of another opiate analgesic has been beneficial.

Inadvertent administration

A sufficient amount of *ULTIVA* may be present in the dead space of the i.v. line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with i.v. fluids or other drugs. This may be avoided by administering *ULTIVA* into a fast-flowing i.v. line or via a dedicated i.v. line which is adequately cleared of residual drug or which is removed upon discontinuation of *ULTIVA*.

Drug abuse

As with other opioids *ULTIVA* may produce dependency.

Interactions

ULTIVA is not metabolised by plasmacholinesterase therefore interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, *ULTIVA* decreases the amounts or doses of inhaled and i.v. anaesthetics, and benzodiazepines required for anaesthesia (*see Dosage and Administration*). If doses of concomitantly administered CNS depressant drugs are not

reduced, patients may experience an increased incidence of adverse effects associated with these agents.

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

The cardiovascular effects of *ULTIVA* (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents.

Pregnancy and Lactation

Pregnancy

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.

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.

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

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.

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.

Adverse Reactions

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.

Post-Marketing 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.

Overdose

Symptoms and Signs

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 is limited to the immediate time period following drug administration. Response to discontinuation of the drug is rapid with return to baseline within 10 minutes.

Treatment

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH06

Mechanisms of Action

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

Pharmacodynamic Effects

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

Pharmacokinetics

Absorption

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

Distribution

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

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 *ULTIVA* 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 *ULTIVA*, the effective biological half-life is 3 to 10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg.

Special Patient Populations

- **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 ^{o}C.

- **Renal impairment**

The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status. The pharmacokinetics of *ULTIVA* 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 *ULTIVA* 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 *ULTIVA* 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 *ULTIVA* 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 *ULTIVA* should be rapid and similar to that seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 to 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 (greater than 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 *ULTIVA* 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.

Pre-Clinical 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 i.v. products and this finding has no relevance for i.v. administration of remifentanil.

Remifentanil, like other opioid agonists, produced increases in action potential duration (APD) in dog isolated Purkinje fibres. For remifentanil, the effects were seen at concentrations of 1 micromolar or higher (which are higher than plasma concentrations seen in clinical practice). There were no effects at a concentration of 0.1 micromolar.

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

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 *ULTIVA* and/or its metabolites during growth and development.

There have been no additional findings of clinical relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

Glycine.
Hydrochloric acid.

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 infusion bag prior to administration.

Administration of *ULTIVA* into the same i.v. line with blood/serum/plasma is not recommended. Non-specific esterase in blood products may lead to the hydrolysis of *ULTIVA* to its inactive metabolite.

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

Shelf-Life

The expiry date is indicated on the packaging.

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.

Nature and Contents of Container

ULTIVA injection for i.v. use is available as:

1 mg remifentanil lyophilised powder in 3 ml vials.

2 mg remifentanil lyophilised powder in 5 ml vials.

5 mg remifentanil lyophilised powder in 10 ml vials.

Instructions for Use/Handling

ULTIVA is stable for 24 hours at room temperature (25°C) after reconstitution and further dilution to 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml in paediatric patients aged 1 year and over) with one of the following i.v. 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 i.v. fluids when administered into running i.v. 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 running i.v. infusion.

The following tables give guidelines for infusion rates of *ULTIVA*.

Table 1 *ULTIVA* for Injection Infusion Rates (ml/kg/h)

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

Table 2 *ULTIVA* for Injection Infusion Rates (ml/h) for a 20 micrograms/ml Solution

Infusion Rate	Patient Weight (kg)						
(micrograms/kg/min)	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 25 micrograms/ml Solution

Infusion Rate	Patient Weight (kg)									
(micrograms/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 50 micrograms/ml Solution

Infusion Rate	Patient Weight (kg)							
(micrograms/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 250 micrograms/ml Solution

Infusion Rate	Patient Weight (kg)							
(micrograms/kg/min)	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

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