Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ultiva 1 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 1 mg remifentanil (as remifentanil hydrochloride).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
A white to off-white, lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ultiva is indicated as an opioid analgesic adjunct for use with other agents during induction and/or maintenance of general anaesthesia in conjunction with controlled ventilation.

Ultiva is indicated for provision of analgesia in mechanically ventilated intensive care patients of 18 years of age and over.

Ultiva is not indicated for use for post-operative analgesia or for use during spontaneous ventilation anaesthesia until further information becomes available.

4.2 Posology and method of administration

Ultiva shall be administered in hospitals 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 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 section 6.6 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 section 4.4).

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

Dilution

Ultiva may be further diluted after reconstitution (see section 6.3 and 6.6 for storage conditions of the reconstituted/diluted product and the recommended diluents).
For manually-controlled infusion Ultiva can be diluted to concentrations of 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).

4.2.1 GENERAL ANAESTHESIA
The administration of Ultiva must be individualised based on the patient's response.

4.2.1.1 Adults

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

Dosing guidelines for adults

INDICATION	**BOLUS INJECTION** (micrograms/kg)	**CONTINUOUS INFUSION** (micrograms/kg/min)	
		Starting Rate	**Range**
Induction of anaesthesia	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

When given by slow bolus injection at induction Ultiva shall 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 and below to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see *Concomitant medication*).

No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with Ultiva.

Induction of anaesthesia: Ultiva should be administered with a reduced dose of 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 slow bolus injection of 1 micrograms /kg given 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 injection is not necessary.

Maintenance of anaesthesia in ventilated patients: 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 slow bolus injections, over not less than 30 seconds may be administered every 2 to 5 minutes.

Concomitant medication: Ultiva decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).
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 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.

Guidance on use in mechanically ventilated intensive care patients is provided in section 4.2.3.

4.2.1.2 Paediatric patients (1 to 12 years of age)
Co-administration of Ultiva and an intravenous anaesthetic agent for induction of anaesthesia has not been studied in detail and is therefore not recommended.

The following doses of Ultiva are recommended for maintenance of anaesthesia:

Dosing guidelines for maintenance of anaesthesia in paediatric patients (1 to 12 years of age)

***CONCOMITANT ANAESTHETIC AGENT**	**BOLUS INJECTION** (micrograms/kg)	**CONTINUOUS INFUSION** (micrograms /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

* co-administration with nitrous oxide/oxygen in a ratio of 2:1

When given by bolus injection 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. For sole administration of nitrous oxide (70%) with Ultiva, typical maintenance infusion rates should be between 0.4 and 3 micrograms/kg/min, and although not specifically studied, adult data suggest that 0.4 micrograms/kg/min is an appropriate starting rate. 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 an increase of haemodynamic effects such as hypotension and bradycardia. No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with Ultiva (see section 4.2.1.1 *General Anaesthesia - Adults - Concomitant medication*).

Guidelines for patient management in the immediate post-operative period

Establishment of alternative analgesia prior to discontinuation of Ultiva:
Due to the very rapid offset of action of Ultiva, no residual 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 discontinuation of Ultiva. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient's surgical procedure and the level of post-operative care anticipated (see section 4.4.).

4.2.1.3 Neonates/infants (aged less than 1 year):
There is limited clinical trial experience of Ultiva in neonates and infants (aged under 1 year old; see section 5.1). 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 (see section 5.2). However, because there are insufficient clinical data, the administration of Ultiva is not recommended for this age group.

Use for Total Intravenous anaesthesia (TIVA): There is limited clinical trial experience of Ultiva for TIVA in infants (see section 5.1). However, there are insufficient clinical data to make dosage recommendations.

4.2.2 CARDIAC ANAESTHESIA

4.2.2.1 Adults

Dosing guidelines for cardiac anaesthesia

INDICATION	BOLUS INJECTION (micrograms/kg)	CONTINUOUS INFUSION (micrograms/kg/min)	
		Starting Rate	Typical Infusion Rates
Induction of anaesthesia	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 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 micrograms/kg/min. The use of bolus injections 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 slow 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 section 5.2 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 and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia. No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with Ultiva (see section 4.2.1.1 *General Anaesthesia* - Adults – Concomitant medication).

Continuation of Ultiva post-operatively to provide 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 (see section 4.2.3.7 for further information on management of intensive care patients).

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. 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, before weaning the patient from the ventilator.

Guidelines for discontinuation of Ultiva:
Due to the very rapid offset of action of Ultiva, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of Ultiva (see section 4.8). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the Ultiva infusion is discontinued. 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. Haemodynamic changes such as hypertension and tachycardia should be treated with alternative agents as appropriate.

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 post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

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

4.2.3. USE IN INTENSIVE CARE

Ultiva can be used for the provision of analgesia in mechanically ventilated intensive care patients of 18 years of age and over. Sedative agents should be used as appropriate.

The safety and efficacy from well-controlled clinical trials of Ultiva in mechanically ventilated intensive care patients has been established for durations up to 3 days (see section 4.2.3.2. and section 5.2). Therefore, the use of Ultiva is not recommended for a duration of treatment greater than 3 days.

In adults, it is recommended that Ultiva is initiated at an infusion rate of 0.1 microgram/kg/min (6 micrograms/kg/h) to 0.15 micrograms/kg/min (9 micrograms/kg/h). The infusion rate should be titrated in increments of 0.025 micrograms/kg/min (1.5 micrograms/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The patient should be regularly assessed and the Ultiva infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min (12 micrograms/kg/h) is reached and sedation is required, 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 micrograms/kg/min (1.5 micrograms/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 in individual patients:-

Dosing Guidelines for use of Ultiva within the Intensive Care Setting

CONTINUOUS INFUSION micrograms/kg/min *(micrograms/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. 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 (6 micrograms/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% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min (15 micrograms/kg/h), maximum 0.74 micrograms/kg/min (45 micrograms/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. Following administration of Ultiva, the possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit *(see Section 4.4 Special warnings and precautions for use*. Therefore, prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents to prevent hyperalgesia and associated haemodynamic changes. These agents must be given at a sufficient time in advance to allow the therapeutic effects of these agents to become established. The range of options for analgesia includes long acting oral, intravenous, or regional analgesics controlled by the nurse or the patient. These techniques should always be titrated to individual patient needs as the infusion of Ultiva is reduced. It is recommended that the choice of agent(s), the dose and the time of administration are planned prior to discontinuation of Ultiva.

There is a potential for the development of tolerance with time during prolonged administration of μ-opioid agonists.

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 microgram/kg/min (6 micrograms/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.

4.2.3.1. Paediatric intensive care patients
There are no data available on use in paediatric patients.

4.2.3.2. Renally-impaired intensive care patients:
No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy, however the clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. (See section 5.2.).

4.2.4. SPECIAL PATIENT POPULATIONS

4.2.4.1 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 shall be 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.
Cardiac Anaesthesia: No initial dose reduction is required (see section 4.2.2.).
Intensive Care: No initial dose reduction is required (see section 4.2.3.)

4.2.4.2. 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.

4.2.4.3. Renal impairment
On the basis of investigations carried out to date, a dose adjustment in patients with impaired renal function including intensive care patients is not necessary.

4.2.4.4. Hepatic impairment

Studies carried out with a limited number of patients with impaired liver function, do not justify any special dosage recommendations. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil (see section 4.4). These patients shall be closely monitored and the dose of Ultiva shall be titrated to individual patient need.

4.2.4.5. Neurosurgery
There is only limited clinical experience in patients undergoing neurosurgery and insufficient information to recommend a dose.

4.2.4.6. 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. In paediatric patients, there are insufficient data to make a dosage recommendation.

Cardiac Anaesthesia: No initial dose reduction is required (see section 4.2.2).

4.3 Contraindications

As glycine is present in the formulation, Ultiva is contraindicated for epidural and intrathecal use (see Preclinical safety data).
Hypersensitivity to the active substance, other fentanyl analogues, or to any of the excipients listed in section 6.1.
Ultiva is contraindicated for use as the sole agent for induction of anaesthesia.

4.4 Special warnings and precautions for use

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

Rapid offset of action/Transition to alternative analgesia
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 discontinuation of Ultiva. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit *(see Section 4.2 Posology and method of administration)*. Prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient's surgical procedure and the level of post-operative care anticipated. When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

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

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 section 4.3).

Discontinuation of treatment and withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy.
Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of Ultiva in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

Muscle rigidity - prevention and management
At the doses recommended muscle rigidity, sometimes severe, may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, slow bolus injections shall 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 - prevention and management
As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, Ultiva shall only be used in areas where facilities for monitoring and dealing with respiratory depression are available. Special care should be taken in patients with respiratory dysfunction. The appearance of respiratory depression shall 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
The risk of cardiovascular effects such as hypotension and bradycardia, which may rarely lead to asystole/cardiac arrest (see section 4.5 and 4.8) may be reduced by lowering 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, hypotensive and elderly patients may be more sensitive to the cardiovascular effects of Ultiva.

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 drugs. This may be avoided by administering Ultiva into a fast flowing IV line or via a dedicated IV line which is removed when Ultiva is discontinued.

Neonates/infants
There is limited data available on use in neonates/infants under 1 year of age (see sections 4.2.1.3 and 5.1).

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality
disorders).

Ultiva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

As with other opioids, Ultiva decreases the doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see section 4.2). 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 concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Co-administration of remifentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Monoamine Oxidase Inhibitors (MAOIs) may increase the risk of serotonin syndrome, a potentially life-threatening condition. Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to remifentanil use.

The cardiovascular effects of Ultiva (hypotension and bradycardia – see sections 4.4 and 4.8) may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents.

After receiving Ultiva, it is advisable that alcoholic drink is avoided.

4.6 Fertility, 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
There are insufficient data to recommend Ultiva for use during labour and caesarean section. It is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child. In case remifentanil is administered nevertheless, the patient and the neonate must be monitored for signs of excess sedation or respiratory depression (see section 4.4).

Breast-feeding
It is not known whether remifentanil is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanilrelated material was found in rat milk after dosing with remifentanil, nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of Ultiva.

4.7 Effects on ability to drive and use machines

After anaesthesia with Ultiva the patient should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that the patient is accompanied when returning home.

4.8 Undesirable effects

Summary of the safety profile
The most common undesirable effects associated with Ultiva are direct extensions of mu-opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil administration.

Tabulated list of adverse reactions
The frequencies below 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), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Immune System Disorders	Rare	Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents
	Not known	Anaphylactic shock
Psychiatric disorders	Not known	Drug dependence, withdrawal syndrome
Nervous System Disorders	Very common	Skeletal muscle rigidity

	Rare	Sedation (during recovery from general anaesthesia)
	Not known	Convulsions
Cardiac Disorders	Common	Bradycardia
	Rare	Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents
	Not known	Atrioventricular block, arrhythmia
Vascular Disorders	Very common	Hypotension
	Common	Post-operative hypertension
Respiratory, Thoracic and Mediastinal Disorders	Common	Acute respiratory depression, apnoea, cough
	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
	Not known	Drug tolerance

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie .

4.9 Overdose

Symptoms
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 drug administration. Response to discontinuation of the drug is rapid, with return to baseline within 10 minutes.

Management
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 vasopressor for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote to manage severe 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 Pharmacodynamic properties

ATC code: N01AH06

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 30 micrograms/kg.

Neonates/infants (aged less than 1 year):

In a randomised (ratio of 2:1, remifentanil:halothane), open label, parallel group, multicentre study in 60 young infants and neonates ≤8 weeks of age (mean 5.5 weeks) with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0.4 µg/kg/min initial continuous infusion plus supplemental doses or infusion rate changes as needed) was compared with halothane (given at 0.4% with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 70% nitrous oxide (N_20) plus 30% oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant).
Use for Total Intravenous anaesthesia (TIVA) - children aged 6 months to 16 years

TIVA with remifenanil in paediatric surgery was compared to inhalation anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical intervention	**Age (y), (N)**	**Study condition (maintenance)**	**Extubation (min) (mean (SD))**
Lower abdominal/urological surgery	0.5-16 (120)	TIVA: propofol (5 - 10 mg/kg/h) + remifentanil (0.125 - 1.0 µg/kg/min)	11.8 (4.2)
		Inhalation anaesthesia: sevoflurane (1.0 - 1.5 MAC) and remifentanil (0.125 - 1.0 µg/kg/min)	15.0 (5.6) ($p<0.05$)
ENT-surgery	4-11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0.5 µg/kg/min)	11 (3.7)
		Inhalation anaesthesia: desflurane (1.3 MAC) and N_2O mixture	9.4 (2.9) Not significant
General or ENT surgery	2-12 (153)	TIVA: remifentanil (0.2 - 0.5 µg/kg/min) + propofol (100 - 200 µg/kg/min)	Comparable extubation times (based on limited data)
		Inhalation anaesthesia: sevoflurane (1 - 1.5 MAC) + N_2O mixture	

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

5.2 Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective half-life is
3-10 minutes. The average clearance of remifentanil in young healthy adults is 40ml/min/kg, the central volume of distribution is 100ml/kg and the steady-state volume of distribution is 350ml/kg. Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 microgram/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5ng/ml. 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 a carboxylic acid metabolite which in dogs is 1/4600th as potent as remifentanil. Studies in man indicate that all pharmacological activity is associated with the parent compound. The activity of this metabolite is therefore not of any clinical consequence. The half-life of the metabolite in healthy adults is 2 hours. In patients with normal renal function, the time for 95% elimination of the primary metabolite of remifentanil by the kidneys, is approximately 7-10 hours. Remifentanil is not a substrate for plasma cholinesterase.

Placental and milk transfer
Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanil and/or its metabolites during growth and development. Remifentanil-related material is transferred to the milk of lactating rats. 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 approximately 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree centigrade.

Renal impairment
In the clinical studies conducted to date, the rapid recovery from remifentanil-based analgesia appears 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 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 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
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 elimination half-life of remifentanil in neonates is not significantly different from that of young healthy adults. Changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to those 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 in elderly patients (>65 years) compared to young patients. The pharmacodynamic activity of remifentanil increases with increasing age. Elderly patients have a remifentanil EC_{50} for 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.

5.3 Preclinical safety data

Acute toxicity
Expected signs of mu-opioid intoxication were observed in non-ventilated mice, rats, and dogs after large single bolus intravenous doses of remifentanil. In these studies, the most sensitive species, the male rat, survived following administration of 5mg/kg. Hypoxia-induced brain microhaemorrhages observed in dogs were reversed within 14 days after completion of dosing.

Repeat dose toxicity
Bolus doses of remifentanil administered to non-ventilated rats and dogs resulted in respiratory depression in all dose groups, and in reversible brain microhaemorrhages in dogs. Subsequent investigations showed that the microhaemorrhages resulted from hypoxia and were not specific to remifentanil. Brain microhaemorrhages were not observed in infusion studies in nonventilated rats and dogs because these studies were conducted at doses that did not cause severe respiratory depression.

It is to be derived from preclinical studies that respiratory depression and associated sequelae are the most likely cause of potentially serious adverse events in humans

Intrathecal administration to dogs of the glycine formulation alone (i.e., without remifentanil) caused agitation, pain and hind limb dysfunction and incoordination. These effects are believed to be secondary to the glycine excipient. Because of the better

buffering properties of blood, the more rapid dilution, and the low glycine concentration of the Ultiva formulation, this finding has no clinical relevance for intravenous administration of Ultiva.

Reproductive toxicity studies
Remifentanil reduced fertility in male rats after daily injection for at least 70 days. A no-effect dose was not demonstrated. Fertility was not affected in female rats. Teratogenic effects were not seen in rats or rabbits. Administration of remifentanil to rats throughout late gestation and lactation did not significantly affect the survival, development, or reproductive performance of the F_1 generation.

Genotoxicity
Remifentanil did not yield positive findings in a series of *in vitro* and *in vivo* genotoxicity tests, except in the *in vitro* mouse lymphoma tk assay, which gave a positive result with metabolic activation. Since the mouse lymphoma results could not be confirmed in further *in vitro* and *in vivo* tests, treatment with remifentanil is not considered to pose a genotoxic hazard to patients.

Carcinogenicity
Long-term carcinogenicity studies were not performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Hydrochloric Acid (for pH adjustment)
Sodium Hydroxide (for pH adjustment if needed)

6.2 Incompatibilities

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

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 intravenous line with blood/serum/ plasma is not recommended as 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

Unopened: 18 months
Following reconstitution/dilution
Chemical and physical in-use stability of the reconstituted solution of Ultiva has been demonstrated for 24 hours at room temperature (25°C). Ultiva should not be administered without further dilution (see section 6.6).
From a microbiological point of view, both the reconstituted product and the diluted product should be used immediately, following preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution had taken place in controlled and validated aseptic conditions. Any unused solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.

For storage instructions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Ultiva injection for intravenous use is available as a glass vial with rubber stopper and aluminium overseal:

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ultiva should be prepared for intravenous use by adding, as appropriate 1, 2 or 5ml of diluent to give a reconstituted solution with a concentration of approximately 1 mg/ml remifentanil. The reconstituted solution is clear, colourless and practically free from particulate material.

After reconstitution, Ultiva should not be administered without further dilution to concentrations of 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 listed below:

The dilution is dependent upon the technical capability of the infusion device and the anticipated requirements of the patient.

- 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 catheter:
- 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 catheter.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The following tables give guidelines for infusion rates of Ultiva:

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

Drug Delivery Rate (µg/kg/min)	**Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of**			
	20µg/ml 1mg/50ml	**25µg/ml** 1mg/40ml	**50µg/ml** 1mg/20ml	**250µg/ml** 10 mg/40ml
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 20µg/ml Solution

Infusion Rate	**Patient Weight** (Kg)						
(µg/kg/min)	**5**	**10**	**20**	**30**	**40**	**50**	**60**
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 25µg/ml Solution

Infusion Rate	**Patient Weight** (Kg)									
(µg/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 50µg/ml Solution

Infusion Rate	**Patient Weight** (kg)							
(µg/kg/min)	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
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 250µg/ml Solution

Infusion Rate	**Patient Weight** (kg)							
(µg/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

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/032/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 1999

Date of last renewal: 27 May 2009

10 DATE OF REVISION OF THE TEXT

June 2024