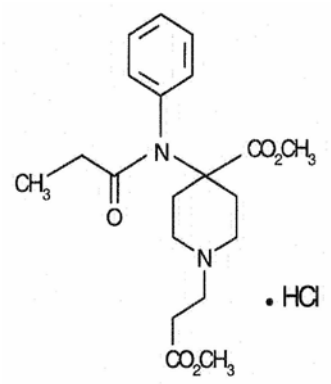
PRODUCT INFORMATION

ULTIVA® (remifentanil hydrochloride) for Injection

NAME OF THE MEDICINE:

The chemical name of remifentanil hydrochloride is 1-(2-Methoxycarbonyl-ethyl)-4-(phenyl-propionyl-amino)-piperidine-4-carboxylic acid methyl ester hydrochloride. The structural formula is given below:



CAS Number: 13539-07-2
Molecular Formula: $C_{20}H_{28}N_2O_5$
Molecular Weight: 412.9

DESCRIPTION:

The log $P_{n\text{-octanol/water}}$ is 17.9. Remifentanil HCl possesses no chiral centres. Ultiva (remifentanil hydrochloride) for Injection is supplied as sterile, non-pyrogenic, preservative-free lyophilised powder for intravenous administration. The product is formulated in glycine and requires reconstitution and dilution before use. Three strengths are available; 1 mg, 2 mg and 5 mg of remifentanil base (as the hydrochloride salt) packed in clear glass vials with siliconised stoppers and overseals.

PHARMACOLOGY:

Pharmacodynamic properties

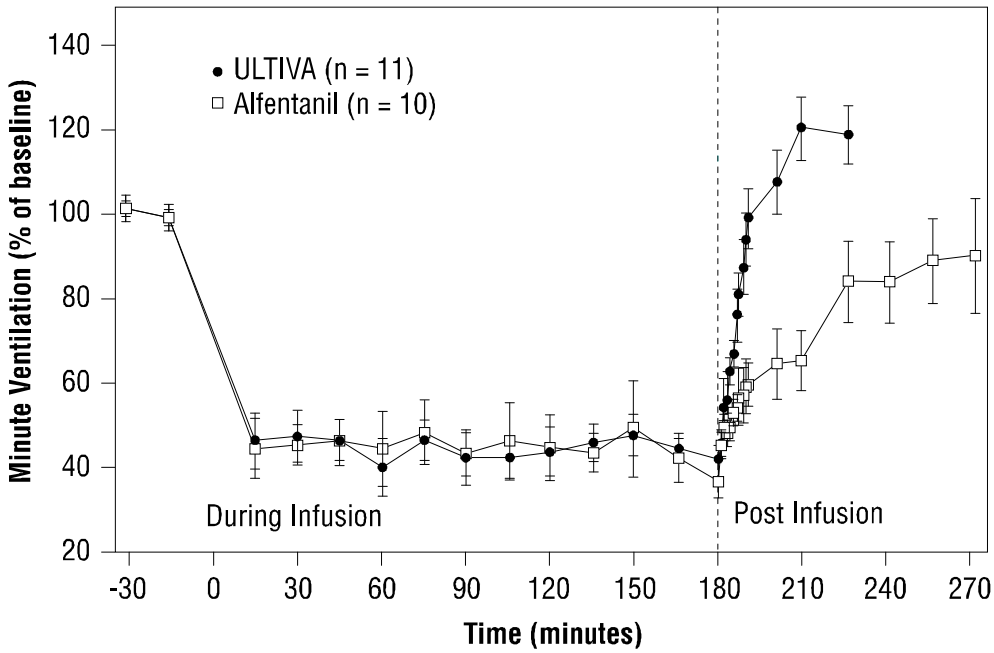
Remifentanil is a potent, selective, 4-anilidopiperidine μ-opioid agonist with pharmacological action typical of this class of compound. It is distinguished from other 4-anilidopiperidines (fentanyl analogues) by its rapid onset and very short duration of action. The μ-opioid activity of remifentanil is antagonised by naloxone. Remifentanil in humans has a rapid blood-brain equilibration half-time of 1 ± 1 minutes (mean ± SD) and a rapid onset of action. The pharmacodynamic effects of remifentanil closely follow the measured blood concentrations, allowing direct correlation between dose, blood levels, and response. Blood concentration decreases 50% in 3 to 6 minutes after a 1-minute infusion or after prolonged continuous infusion due to rapid distribution and elimination processes and is independent of duration of drug administration. Recovery from the effects of remifentanil occurs rapidly (within 5 to 10 minutes). New steady-state concentrations occur within 5 to 10 minutes after changes in infusion rate. When used as a component of an anaesthetic technique, remifentanil can be

rapidly titrated to the desired depth of anaesthesia/analgesia (e.g., as required by varying levels of intraoperative stress) by changing the continuous infusion rate or by administering an IV bolus injection. Remifentanil is a potent opioid, therefore careful adherence to the **PRECAUTIONS** and **DOSAGE and ADMINISTRATION** sections of the document is essential to avoid unacceptable adverse events.

Haemodynamics: In premedicated patients undergoing anaesthesia, 1-minute infusions of <2 μg/kg of remifentanil caused dose-dependent hypotension and bradycardia. While additional doses >2 μg/kg (up to 30 μg/kg) do not produce any further decreases in heart rate or blood pressure, the duration of the haemodynamic change is increased in proportion to the blood concentrations achieved. Peak haemodynamic effects occur within 3 to 5 minutes of a single dose of remifentanil or an infusion rate increase. Glycopyrrolate, atropine, and vagolytic neuromuscular blocking agents attenuate the haemodynamic effects associated with remifentanil. When appropriate, bradycardia and hypotension can be reversed by reduction of the rate of infusion of remifentanil, or the dose of concurrent anaesthetics, or by the administration of fluids or vasopressors.

Respiration: Remifentanil depresses respiration in a dose-related fashion. Unlike other fentanyl analogues, the duration of action of remifentanil at a given dose does not increase with increasing duration of administration, due to lack of drug accumulation. When remifentanil and alfentanil were dosed to equal levels of respiratory depression, recovery of respiratory drive after 3-hour infusions was more rapid and less variable with remifentanil (see Figure 1).

Figure 1: Recovery of Respiratory Drive after Equipotent* Doses of Remifentanil (ULTIVA) and Alfentanil using CO_2-Stimulated Minute Ventilation in Volunteers (± 1.5 SEM)



The infusion rates used in this study were 0.025 – 0.062 μg/kg/min for Ultiva and 0.19 – 0.48 μg/kg/min for alfentanil.
*Equipotent refers to level of respiratory depression

Spontaneous respiration occurs at blood concentrations of 4 to 5 ng/mL in the absence of other anaesthetic agents, for example, after discontinuation of a 0.25 μg/kg/min infusion of remifentanil, these blood concentrations would be reached in 2 to 4 minutes. In patients undergoing general anaesthesia, the rate of respiratory recovery depends upon the concurrent anaesthetic; it is fastest after N_2O, slower with propofol, and slowest after isoflurane.

Muscle Rigidity: Skeletal muscle rigidity can be caused by remifentanil and is related to the dose and speed of administration. Remifentanil may cause chest wall rigidity (inability to ventilate) after single doses of >1 μg/kg administered over 30 to 60 seconds or infusion rates >0.1 μg/kg/min. Administration of doses < 1 μg/kg may cause chest wall rigidity when given concurrently with a continuous infusion of remifentanil.

Histamine release: Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after administration of remifentanil in doses up to 30 μg/kg over 60 seconds.

Pharmacokinetic properties

Absorption

Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 μg/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5 ng/mL. Unlike other fentanyl analogues, the duration of action does not increase with prolonged administration.

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. It is rapidly and extensively metabolised by non-specific esterases in blood and tissues to the carboxylic acid derivative, GR90291. This metabolite is 4,600 times less active than the parent compound in quantitative EEG analysis of opioid activity.

It is unlikely that there is any clinically significant activity of the metabolite. The half-life of the metabolite in healthy adults is 2 hours. Approximately 95% of remifentanil is recovered in the urine as the carboxylic acid metabolite. Remifentanil is not a substrate for plasma cholinesterase.

Excretion

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes due to redistribution. The terminal half-life of the unchanged drug is 10 to 20 minutes. The average clearance of remifentanil in young healthy adults is 40 mL/min/kg. Clearance generally correlates with total body weight (with the exception of severely obese patients in whom it correlates with ideal body weight).

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^{o}C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree Celsius.

Pharmacokinetics in patients with renal impairment
After 72 hours of infusion, the rapid recovery from remifentanil-based sedation and analgesia is unaffected by mild renal impairment and may be slightly prolonged in patients with moderate/severe renal impairment (median time to off-set of effects of remifentanil was 30 minutes in patients with moderate/severe renal impairment compared with 13.5 minutes in mild renal impairment).

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. There is no evidence that the metabolite produces clinically relevant μ-opioid effects even after administration of remifentanil infusions for up to three days in these patients. However, due to the limited data available, it is not known whether the accumulated metabolite has any other clinically relevant effects. (see **CLINICAL TRIALS – Intensive Care Unit**).

There is no evidence that remifentanil is extracted during renal replacement therapy.

The carboxylic acid metabolite is extracted during haemodialysis by at least 30%.

Pharmacokinetics in patients with 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. Individuals with severe hepatic impairment demonstrated statistically significant, reduced sensitivity to carbon dioxide stimulation of minute ventilation, which may indicate an increased sensitivity 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's need.

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

Pharmacokinetics in elderly patients

The clearance of remifentanil is reduced (approximately 25%) in elderly patients (>65 years) compared to young patients. The pharmacodynamic activity of remifentanil increases with increasing age. The EC_{50} for formation of delta waves on the electroencephalogram (EEG) in elderly patients receiving remifentanil is 50% lower than in 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's need.

CLINICAL TRIALS:

Clinical trials have demonstrated that remifentanil is unsuitable as a sole agent for induction. For induction, remifentanil should only be used as an opioid adjunct where intubation and mechanical ventilation are intended. Remifentanil is not recommended for use in post-operative analgesia, except for ventilated cardiac surgery patients in an environment where the patient is under the close supervision of medically qualified persons trained in the use of anaesthetic drugs **(see INDICATIONS and CONTRAINDICATIONS)**.

Ultiva was evaluated in 3,562 patients undergoing general anaesthesia (n = 2,923) and monitored anaesthesia care (n = 639). These patients were evaluated in the following settings: inpatient (n = 2,213) which included cardiovascular (n = 675) and neurosurgical (n = 61), and outpatient (n = 1,349). Three hundred seventy-seven (377) elderly patients (age range 66 to 90 years) and 440 paediatric patients received Ultiva. Of the general anaesthesia patients, 1,132 also received Ultiva as an IV analgesic agent during the immediate post-operative period.

Induction and Maintenance of General Anaesthesia - Inpatient/Outpatient: The efficacy of Ultiva was investigated in 1562 patients in 15 randomised, controlled trials as the analgesic component for the induction and maintenance of general anaesthesia. Eight of these studies compared Ultiva to alfentanil, and two studies compared Ultiva to fentanyl. In these studies, doses of Ultiva up to the ED90 were compared to recommended doses (approximately ED50) of alfentanil or fentanyl.

Induction of Anaesthesia: Ultiva was administered with isoflurane, propofol, or thiopentone for the induction of anaesthesia (n = 1,562). The majority of patients (80%) received propofol as the concurrent agent. Ultiva reduced the propofol and thiopentone requirements for loss of consciousness. Compared to alfentanil and fentanyl, a higher relative dose of Ultiva resulted in fewer responses to intubation (see Table 1). Overall, hypotension occurred in 5% of patients receiving Ultiva compared to 2% of patients receiving the other opioids.
Ultiva has been used as a primary agent for the induction of anaesthesia; however, it should not be used as a sole agent because loss of consciousness cannot be assured and because of a high incidence of apnoea, muscle rigidity, and tachycardia. The administration of an induction dose of propofol or thiopentone or a paralysing dose of a muscle relaxant prior to or concurrently with Ultiva during the induction of anaesthesia markedly decreased the incidence of muscle rigidity from 20% to <1%.

Table 1: Response to Intubation (Propofol/Opioid Induction*)

Opioid Treatment Group/(No. of Patients)	Initial Dose (µg/kg)	Pre-Intubation Infusion Rate (µg/kg/min)	No. (%) Muscle Rigidity	No. (%) Hypotension During Induction	No. (%) Response to Intubation
Study 1:					
Ultiva (35)	1	0.1	1 (3%)	0	27 (77%)
Ultiva (35)	1	0.4	3 (9%)	0	11 (31%)†
Alfentanil (35)	20	1.0	2 (6%)	0	26 (74%)
Study 2:					
Ultiva (116)	1	0.5	9 (8%)	5 (4%)	17 (15%)†
Alfentanil (118)	25	1.0	6 (5%)	5 (4%)	33 (28%)
Study 3:					
Ultiva (134)	1	0.5	2 (1%)	4 (3%)	25 (19%)
Alfentanil (66)	20	2.0	0	0	19 (29%)
Study 4:					
Ultiva (98)	1	0.2	11 (11%)†	2 (2%)	35 (36%)
Ultiva (91)	2‡	0.4	11 (12%)†	2 (2%)	12 (13%)†
Fentanyl (97)	3	NA	1 (1%)	1 (1%)	29 (30%)

* Propofol was titrated to loss of consciousness.

† Differences were statistically significant ($P < 0.02$).

‡ Initial doses greater than 1 µg/kg are not recommended.

Use During Maintenance of Anaesthesia: Ultiva was investigated in 929 patients in seven well-controlled general surgery studies in conjunction with nitrous oxide, isoflurane, or propofol in both inpatient and outpatient settings. These studies demonstrated that Ultiva could be dosed to high levels of opioid effect and rapidly titrated to optimise analgesia intraoperatively without delaying or prolonging recovery. Remifentanil was inadequate as a sole agent for maintenance of anaesthesia.

Compared to alfentanil and fentanyl, these higher relative doses (ED90) of Ultiva resulted in fewer responses to intraoperative stimuli (see Table 2) and a higher frequency of hypotension (16% compared to 5% for the other opioids). Ultiva was infused to the end of surgery, while alfentanil was discontinued 5 to 30 minutes before the end of surgery as recommended. The mean final infusion rates of Ultiva were between 0.25 and 0.48 µg/kg/min.

Table 2: Intraoperative Responses*

Opioid Treatment Group/(No. of Patients)	Concurrent Anaesthetic	Post-Intubation Infusion Rate (µg/kg/min)	No. (%) With Intraoperative Hypotension	No. (%) With Response to Skin Incision	No. (%) With Signs of Light Anaesthesia	No. (%) With Response to Skin Closure
Study 1:						
Ultiva (35)		0.1	0	20 (57%)	33 (94%)	6 (17%)
Ultiva (35)	Nitrous oxide	0.4	0	3 (9%)†	12 (34%)†	2 (6%)†
Alfentanil (35)		1.0	0	24 (69%)	33 (94%)	12 (34%)
Study 2:						
Ultiva (116)	Isoflurane +	0.25	35 (30%)†	9 (8%)†	66 (57%)†	19 (16%)
Alfentanil (118)	Nitrous oxide	0.5	12 (10%)	20 (17%)	85 (72%)	25 (21%)
Study 3:						
Ultiva (134)	Propofol	0.5	3 (2%)	14 (11%)†	70 (52%)†	25 (19%)
Alfentanil (66)		2.0	2 (3%)	21 (32%)	47 (71%)	13 (20%)
Study 4:						
Ultiva (98)		0.2	13 (13%)	12 (12%)†	67 (68%)†	7 (7%)
Ultiva (91)	Isoflurane	0.4	16 (18%)†	4 (4%)†	44 (48%)†	3 (3%)†
Fentanyl (97)		1.5-3 µg/kg prn	7 (7%)	32 (33%)	84 (87%)	11 (11%)

* Not all doses of Ultiva were equipotent to the comparator opioid.

† Differences were statistically significant ($P < 0.05$).

In three randomised, controlled studies (n = 407) during general anaesthesia, Ultiva attenuated the signs of light anaesthesia within a median time of 3 to 6 minutes after bolus doses of 1 µg/kg with or without infusion rate increases of 50% to 100% (up to a maximum rate of 2 µg/kg/min).

In an additional double-blind, randomised study (n = 103), a constant rate (0.25 µg/kg/min) of Ultiva was compared to doubling the rate to 0.5 µg/kg/min approximately 5 minutes before the start of the major surgical stress event. Doubling the rate decreased the incidence of signs of light anaesthesia from 67% to 8% in patients undergoing abdominal hysterectomy, and from 19% to 10% in patients undergoing radical prostatectomy. In patients undergoing laminectomy the lower dose was adequate.

Recovery: In 2,169 patients receiving Ultiva for periods up to 16 hours, recovery from anaesthesia was rapid, predictable, and independent of the duration of the infusion of Ultiva. In the seven controlled, general surgery studies, extubation occurred in a median of 5 minutes (range: -3 to 17 minutes in 95% of patients) in outpatient anaesthesia and 10 minutes (range: 0 to 32 minutes in 95% of patients) in inpatient anaesthesia. Recovery in studies using nitrous oxide or propofol was faster than in those using isoflurane as the concurrent

anaesthetic. There was no case of remifentanil-induced delayed respiratory depression (occurring more than 30 minutes after discontinuation of remifentanil).

In a double-blind, randomised study, administration of morphine sulfate (0.15 mg/kg) intravenously 20 minutes before the anticipated end of surgery to 98 patients did not delay recovery of respiratory drive in patients undergoing major surgery with remifentanil-propofol total IV anaesthesia.

Paediatric Anaesthesia: The safety, efficacy and pharmacokinetics of Ultiva have been established in five studies which included 687 paediatric patients (aged 5 days to 17 years). Of these, 437 patients received Ultiva: 65 patients were enrolled in pharmacokinetic studies and 372 paediatric patients were studied undergoing general anaesthesia for routine surgical procedures in the inpatient (n=190) and outpatient (n=182) settings. Two hundred and fifty patients were administered comparator anaesthetic regimens. Four of the these studies were open-labelled.

One randomised, double-blind, parallel comparator-controlled study consisted of 206 patients, of which 103 received Ultiva. This study found the median time to extubation was 9 minutes vs. 10 minutes for fentanyl. The overall incidences of adverse events were 38% for Ultiva and 39% for fentanyl, drug-related adverse events were 19% and 22% respectively.

The studies confirmed the effectiveness of the initial adult dosing in paediatric patients >1 year of age with subsequent titration to clinical effect according to individual patient requirements. Ultiva-based anaesthesia was shown to be as effective as conventional anaesthetic regimens in attenuation of responses to stimulating procedures and the provision of intra-operative haemodynamic stability. Ultiva could be continued until the end of surgery and recovery from anaesthesia was rapid, predictable and similar to conventional anaesthetic regimens. Generally higher post-operative pain scores were observed when using Ultiva, consistent with the rapid offset of action of Ultiva. This highlights that longer acting analgesia must be established at an appropriate time in advance of the discontinuation of Ultiva to minimise post-operative pain (see Guidelines for discontinuation).

No relationship was found between age and the final infusion rate of Ultiva, indicating that the starting dose was appropriate across the range of ages studied. There were no clinically significant differences in time to extubation or other recovery parameters between Ultiva-based anaesthesia and conventional anaesthetic regimens. Ultiva was well tolerated and the incidence of adverse events at the recommended maintenance doses in combination with inhalational anaesthetics was similar to that reported in adults.

Cardiac Surgery: In preliminary investigations of cardiac anaesthesia, two studies evaluated the pharmacokinetics of Ultiva in patients (n=25) undergoing hypothermic CABG surgery; and two dose ranging studies were conducted which included a total of 217 ASA II-IV patients undergoing CABG surgery. The data indicated that high dose Ultiva (starting doses 1-3μg/kg/min) effectively attenuated responses to major surgical stress and was associated with a rapid recovery profile. However, none of these studies included comparator opioids.

Subsequently Ultiva was evaluated in four randomised, double blind studies including a total of 830 patients (450 Ultiva, 380 comparator opioid) undergoing coronary artery bypass graft (CABG) or valve replacement/repair surgery. This was initiated to develop dosing guidelines for use of Ultiva in cardiac patients, establish the safety and efficacy of Ultiva compared with the use of fentanyl and sufentanil in 'fast-track' cardiac anaesthesia; and especially in 'higher risk' cardiac patients – those with impaired left ventricular function (ejection fraction <0.35) or undergoing valve surgery.

A high dose Ultiva-based regimen was generally more effective in attenuating major surgical stress responses compared to conventional opioid regimens (low/medium intermittent dose)

used for 'fast-track' cardiac surgery (e.g. attenuation of response to Maximal Sternal Spread was 11-21% with Ultiva vs. 44-52% fentanyl and 39% sufentanil). Comparable haemodynamic stability was observed during surgery with Ultiva and comparator opioid regimens. After induction and during maintenance, remifentanil was associated with a higher incidence of hypotension or requirement for treatment of excessive anaesthesia than comparator opioid regimens.

Continuation of an Ultiva regimen at a fixed rate of 1μg/kg/min into the immediate post-operative period (ICU) was effective in managing patient comfort. The protocol regimen for transition to alternative analgesia in advance of down titration and discontinuation from Ultiva during weaning for extubation, was effective. Although sedation was increased it did not result in significant delay in post-operative recovery. Times to discharge from an intensive care setting were comparable to 'fast-track' opioid regimens.

For the side-effect profile in cardiac surgery, refer to **ADVERSE EFFECTS.**

Neurosurgery: Ultiva was administered to 61 patients undergoing craniotomy for removal of a supratentorial mass lesion. In these studies, ventilation was controlled to maintain a predicted PaCO2 of approximately 28 mmHg. In one study (n = 30) with Ultiva and 66% nitrous oxide, the median time to extubation and to patient response to verbal commands was 5 minutes (range-1 to 19 minutes). Intracranial pressure and cerebrovascular responsiveness to carbon dioxide were normal.

A randomised, controlled study compared Ultiva (n = 31) to fentanyl (n = 32). Ultiva (1 μg/kg/min) and fentanyl (2 μg/kg/min) were administered after induction with thiopentone and pancuronium. A similar number of patients (6%) receiving Ultiva and fentanyl had hypotension during induction. Anaesthesia was maintained with nitrous oxide and Ultiva at a mean infusion rate of 0.23 μg/kg/min (range 0.1 to 0.4) compared with a fentanyl mean infusion rate of 0.04 μg/kg/min (range 0.02 to 0.07). Supplemental isoflurane was administered as needed. The patients receiving Ultiva required a lower mean isoflurane dose (0.07 MAC-hours) compared with 0.64 MAC-hours for the fentanyl patients (P = 0.04). Ultiva was discontinued at the end of anaesthesia, whereas fentanyl was discontinued at the time of bone flap replacement (a median time of 44 minutes before the end of surgery). Median time to extubation was similar (5 and 3.5 minutes, respectively, with Ultiva and fentanyl). None of the patients receiving Ultiva required naloxone compared to seven of the fentanyl patients (P = 0.01). Eighty-one percent (81%) of patients receiving Ultiva recovered (awake, alert, and oriented) within 30 minutes after surgery compared with 59% of fentanyl patients (P = 0.06). At 45 minutes, recovery rates were similar (81% and 69% respectively for Ultiva and fentanyl, P = 0.27). Patients receiving Ultiva required an analgesic for headache sooner than fentanyl patients (median of 35 minutes compared with 136 minutes, respectively [P = 0.04]). No adverse cerebrovascular effects were seen in this study.

Intensive Care Unit: Three clinical studies were conducted to determine the safety and efficacy of remifentanil in a clinically relevant Intensive Care population requiring mechanical ventilation for up to three days. Two of these studies (USA03206 & USA 30207) were randomised, double-blind, controlled, parallel group studies, the third of these (USA 30212) was an open labelled, non-comparator study. A total of 261 patients received remifentanil, 81 received fentanyl and 83 received morphine. Of those receiving remifentanil, 32 were treated for ≥48 hours, 12 of whom had moderate/severe renal impairment.

The randomized, double-blind studies compared a remifentanil-based analgesia/sedation regimen with fentanyl or morphine based regimens. The opioid was initially titrated to achieve adequate levels for sedation (a patient who was calm, easily rousable and followed commands) and analgesia (no or mild pain). Frequent monitoring of the depth of sedation and

analgesia was undertaken. Administration of sedative agent was initiated only if the target level of sedation could not be achieved with opioid alone.

A remifentanil-based regimen was effective in providing optimal sedation for the majority (82%-90%) of the maintenance phase. Fentanyl and morphine comparator regimens provided similar efficacy in terms of duration of optimal sedation. Remifentanil infusion alone provided optimal sedation in the majority (65% in USA30206, 78% in USA30207 and 43% in USA30212) of patients without the need for a supplementary sedative agent.

The primary end point, between patient variability in the percentage of hours of optimal sedation, was not statistically significantly different for remifentanil compared with fentanyl (study USA30206) or morphine (study USA30207).

Remifentanil was effective in providing adequate analgesia (no pain/mild pain) for the majority (>94%) of the maintenance phase. Fentanyl and morphine provided similar efficacy in terms of duration of adequate analgesia. Moderate/severe pain was reported in a higher percentage of patients administered remifentanil compared to those administered morphine and fentanyl subsequent to down titration and discontinuation of the opioid. This was consistent with the rapid offset of the analgesic effects of remifentanil.

The time to extubation was rapid and comparable between remifentanil and the comparator regimens (median values ≤1.3h in studies USA30206 and USA30207).

Remifentanil was associated with acceptable haemodynamic stability during the maintenance phase, which was similar to that observed in patients administered morphine or fentanyl. A greater incidence of haemodynamic changes were reported in the extubation, post-extubation and post-treatment phases in the remifentanil group, which were related to a greater incidence of pain.

The data indicate that a remifentanil-based regimen (starting infusion rate 0.1-0.15µg/kg/min), was very effective for establishing and maintaining optimal analgesia and sedation in a wide range of IC patients, including those with severe renal impairment. In the majority of patients (≥60%) in the comparator studies there was no requirement for infusion of supplementary sedative agents (midazolam or propofol) to maintain optimal sedation (SAS 4). In study USA30212, where patients could be more deeply sedated (SAS 2-4), there was a greater requirement for supplementary use of sedative i.e. 58% of patients required propofol infusion. Use of a remifentanil-based regimen resulted in rapid extubation of the patients, similar to the comparator opioid regimens.

INDICATIONS:

Ultiva for Injection is indicated -

- as an opioid adjunct for use during induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery in adults.
- As an opioid adjunct for use during induction and/or maintenance of general anaesthesia during surgical but not cardiac procedures in children aged 1 to 12 years.
- for continuation as an analgesic into the immediate post-operative period under the close supervision of medically qualified persons trained in the use of anaesthetic drugs, during transition to longer acting analgesia following adult cardiac surgery - when endotracheal intubation and controlled ventilation are anticipated.
- for provision of analgesia and sedation in mechanically ventilated intensive care patients.

CONTRAINDICATIONS:

Ultiva is not suitable as the sole agent for induction of general anaesthesia.

Ultiva is not recommended for use in spontaneous ventilation anaesthesia or as an analgesic in the immediate post-operative period due to inadequate safety data in such uses, except in ventilated cardiac surgery patients (see INDICATIONS and DOSAGE and ADMINISTRATION: 2. Cardiac Anaesthesia).

As glycine is present in the formulation, Ultiva is contraindicated for epidural and intrathecal use.

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

PRECAUTIONS:

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

The use of Ultiva may be associated with apnoea and respiratory depression. Ultiva should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by medically qualified 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 intubation and assisted ventilation.

Muscle rigidity - prevention and management

At the recommended doses, Ultiva can cause muscle rigidity. Profound chest wall rigidity and inability to ventilate the patient has occurred during induction, and following inadvertent boluses after intravenous line flushing. The incidence of muscle rigidity is related to the dose and rate of administration. Therefore, boluses should be administered slowly, over 60 seconds.

Muscle rigidity induced by Ultiva must be treated in the context of the patient's clinical condition with appropriate supporting measures. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents and may require intubation for ventilation. 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. In the case of life-threatening muscle rigidity, a rapid onset neuromuscular blocker or an opioid antagonist may be administered.

Respiratory depression - management

The use of Ultiva may be associated with apnoea and respiratory depression. Therefore Ultiva should only be used where facilities for monitoring and treating respiratory depression are available. The occurrence of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50% or a temporary discontinuation of the infusion. Ultiva has not been shown to cause recurrent respiratory depression even after

prolonged administration. However, respiratory depression may occur in some patients up to 30 minutes after cessation of the Ultiva infusion due to residual effects of concomitant anaesthetics, and therefore it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area **(see also Inadvertent administration).**

Cardiovascular effects

Ultiva causes dose-dependent hypotension and bradycardia. These effects may be attenuated by the pre-administration of an appropriate anticholinergic agent such as glycopyrrolate or atropine. Hypotension and bradycardia may be managed by reducing the rate of infusion of Ultiva or the dose of concurrent anaesthetics, and by using intravenous 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

Within 5 to 10 minutes after the discontinuation of Ultiva no residual opioid activity will be present. For those patients undergoing surgical procedures where post-operative pain is generally anticipated alternative analgesics should be administered prior to the 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 follow-up care.

Discontinuation of Treatment

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

Inadvertent administration

A sufficient amount of Ultiva may be present in the dead space of the IV line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with IV fluids or other drugs. Ultiva should be administered, where possible via a dedicated IV line which is removed when Ultiva is discontinued, otherwise into a fast flowing IV line at or close to the venous cannula and primed, in order to avoid administration of drug into the single dead space.

Paediatric patients under 1 year of age

There are insufficient data available on use in paediatric patients under 1 year of age.

Drug Abuse

As with other opioids, Ultiva may produce dependency.

Awareness

Intraoperative awareness has been reported when remifentanil has been administered with propofol infusion rates less than 75 μg/kg/min for TIVA.

Carcinogenicity, mutagenicity and impairment of fertility

There is no information currently available on the carcinogenic potential of remifentanil.

Remifentanil was not mutagenic in bacterial assays for gene mutations (*Salmonella typhimurium* histidine reversion assay), chromosomal aberrations (mouse micronucleus and Chinese hamster ovary chromosome) and a DNA repair assay (rat hepatocytes). However, a positive result was obtained in the mouse lymphoma L5178Y/$tk^{+/-}$ assay in the presence of metabolic activation.

Daily administration of remifentanil to male rats was associated with pathological changes in the epididymides at exposures to remifentanil and its major metabolite GR90291 of <1 and >200 fold, respectively, the anticipated clinical exposure, and pathological changes in the testes and reduced fertility and pregnancies at exposures to remifentanil and GR90291 of 1-2 and >600 fold, respectively, the anticipated clinical exposure.

Use in Pregnancy

Pregnancy Category: C

Although placental transfer of remifentanil and its major metabolite GR90291 was found in rats, rabbits and monkeys, there was no evidence of teratogenicity in rats at exposures to remifentanil and its major metabolite of 6 and >200 fold, respectively, the anticipated clinical exposure. In rabbits, teratogenicity was observed only at remifentanil doses greater than those producing maternotoxicity and fetotoxicity, with remifentanil exposures of about 200 fold anticipated human remifentanil exposure. However, there are no adequate and well-controlled studies in pregnant women. The use of Ultiva in pregnant women is not recommended.

Use in Lactation

It is not known whether Ultiva 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 Ultiva, caution should be exercised when Ultiva is administered to mothers who are breastfeeding.

Use in Obstetrics

The safety profile of Ultiva during labour or delivery has not been demonstrated. Ultiva should not be used during labour and caesarean sections because it is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the infant.

Effects on the ability to drive and operate machinery

Following treatment using anaesthetic agents, patients should be advised not to drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES:

Ultiva is not metabolised by plasma cholinesterase therefore interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, Ultiva decreases the dose of inhaled and intravenous 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.

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.

ADVERSE EFFECTS:

The most common adverse events associated with remifentanil are direct extensions of μ-opioid agonist pharmacology, such as respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. These are dose dependent events and hence dissipate within minutes of discontinuing or decreasing the infusion rate of Ultiva. Hypotension may be relatively more common in the elderly (>65 years).

Approximately 3,800 patients have been exposed to Ultiva in controlled clinical trials.

The frequencies of adverse events during general anaesthesia with the recommended doses of Ultiva are given in Table 3. Each patient was counted once for each type of adverse event.

Table 3: Adverse Events Reported in ≥ 1% of Patients in General Anaesthesia Studies at the Recommended Doses of Ultiva*

Adverse Event	Induction/Maintenance		After Discontinuation	
	Ultiva	Alfentanil/ Fentanyl	Ultiva	Alfentanil/Fentanyl
	(n = 921)	(n = 466)	(n = 929)	(n = 466)
GASTROINTESTINAL				
Nausea	<1%	0	36%	43%
Vomiting	<1%	<1%	16%	20%
CARDIOVASCULAR				
Hypotension	19%	6%	2%	2%
Bradycardia	7%	5%	1%	1%
Hypertension	1%	2%	1%	2%
Tachycardia	<1%	2%	1%	2%
RESPIRATORY				
Respiratory Depression	<1%	0	2%	4%
Apnoea	0	<1%	<1%	<1%
Hypoxia	0	0	1%	2%
MUSCULOSKELETAL				
Muscle Rigidity	11%#	8%	<1%	<1%
Shivering	<1%	0	5%	2%
NEUROLOGICAL				
Fever	<1%	0	5%	2%
Dizziness	0	0	3%	2%
Visual disturbance	0	0	3%	3%
Headache	0	0	2%	2%
Post-operative Pain	0	0	<1%	1%
Agitation	<1%	0	<1%	<1%
DERMATOLOGICAL				
Pruritus	<1%	0	2%	2%

The doses of comparator opioids used in these studies were as follows:

- Alfentanil: 20 - 50 μg/kg bolus + 0.5 - 2 μg/kg/min infusion.

- Fentanyl: 3 μg/kg bolus + 1.5 - 3 μg/kg bolus doses as required.

***** See Table 4 for recommended doses of Ultiva. Not all doses of Ultiva were equipotent to the comparator opioid. Administration of Ultiva in excess of the recommended dose (i.e., doses >1 and up to 20 μg/kg) resulted in a higher incidence of some adverse events: muscle rigidity (37%), bradycardia (12%), hypertension (4%), and tachycardia (4%).

Included in the muscle rigidity incidence is chest wall rigidity (5%). The overall muscle rigidity incidence is <1% when remifentanil is administered concurrently or after a hypnotic induction agent.

Cardiac Anaesthesia: The side-effect profile of Ultiva was consistent with the known pharmacology of μ-opioid agonists. Hypotension observed in maintenance regimens (4% vs. 1%); and hypertension (2% vs. 0%), shivering (4% vs. 2%) and aches (2% vs. 0%) observed post-operatively; occurred at a greater frequency with remifentanil compared to "fast-track" comparator opioid (fentanyl and sufentanil) regimens. Although there was a higher frequency of the above adverse events, the incidence of adverse cardiac outcomes in each of the randomised, double-blind trials was similar for remifentanil and comparator opioid.

Paediatric Anaesthesia: Ultiva was well tolerated and the incidence of adverse events at the recommended doses was similar to that reported for adults.

Intensive Care Unit: The overall incidence of drug-related adverse events across treatment groups was: remifentanil 22% vs. fentanyl 17% vs. morphine 16%. The incidence of hypotension was comparable between groups (remifentanil 9% vs. fentanyl 9% vs. morphine 7%); the majority of hypotensive reports being drug-related (remifentanil 6% vs. fentanyl 6% vs. morphine 6%). Episodes of hypotension (defined as a mean arterial pressure, 50 mmHg) were more frequent with remifentanil (11% - 17% compared with morphine 2% and fentanyl 10%) however this was not associated with an increase in adverse event reporting. (see **PRECAUTIONS – Cardiovascular effects**). In the remifentanil group the majority of drug-related episodes of hypotension were mild or moderate in severity and in the majority of cases, the average duration was less than 20 minutes.

Pruritus was one of the most commonly reported drug-related adverse events in the remifentanil group (2% incidence).

Other Adverse Events: Less commonly reported adverse clinical events **(incidence < 1%)** from all controlled studies are presented below:

Digestive: constipation, abdominal discomfort, xerostomia, gastro-oesophageal reflux, dysphagia, diarrhoea, heartburn, ileus.

Cardiovascular: various atrial and ventricular arrhythmias, heart block, ECG change consistent with myocardial ischaemia, elevated CPK-MB level, syncope.

Musculoskeletal: muscle stiffness, musculoskeletal chest pain, post-operative aches.

Respiratory: cough, dyspnoea, bronchospasm, laryngospasm, rhonchi, stridor, nasal congestion, pharyngitis, pleural effusion, hiccups, pulmonary oedema, rales, bronchitis, rhinorrhoea.

Nervous: anxiety, involuntary movement, prolonged emergence from anaesthesia, confusion, awareness under anaesthesia without pain, rapid awakening from anaesthesia,

tremors, disorientation, dysphoria, nightmares, hallucinations, paraesthesia, nystagmus, twitch, sleep disorder, seizure, amnaesia

Body as a whole: decreased body temperature, anaphylactic reaction, delayed recovery from neuromuscular block.

Skin: rash, urticaria.

Urogenital: urine retention, oliguria, dysuria, urine incontinence.

Infusion site reactions: erythema, pruritus, rash.

Metabolic and nutrition: abnormal liver function, hyperglycaemia, electrolyte disorders, increased CPK level.

Haematologic and Lymphatic: anaemia, lymphopaenia, leukocytosis, thrombocytopaenia.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of remifentanil in conjunction with one or more anaesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to remifentanil:

Non-site specific: Very rarely, allergic reactions including anaphylaxis have been reported in patients receiving Ultiva in conjunction with one or more anaesthetic agents**.**

Cardiovascular: Rare cases of asystole/cardiac arrest, usually preceded by bradycardia, have been reported in patients receiving remifentanil in conjunction with other anaesthetic agents.

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 medically qualified 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 intubation, and assisted ventilation.

Continuous infusions of Ultiva must be administered by a calibrated infusion device, where possible via a dedicated intravenous line, otherwise into a fast flowing IV line. The Ultiva infusion line should be connected at, or close to, the intravenous cannula and primed, to minimise the potential dead space (see **INSTRUCTIONS FOR USE** 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 **PRECAUTIONS**). Failure to clear the intravenous tubing to remove residual Ultiva has been associated with the appearance of respiratory depression, apnoea and muscle rigidity upon later administration of fluids or medications through the same IV tubing.

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

Administration by Manually-Controlled Infusion

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).

Administration by Target-Controlled Infusion

Ultiva may **also** be given by **target-controlled infusion (TCI) with an approved infusion device incorporating** a validated pharmacokinetic model (**the Minto pharmacokinetic model with covariates for age and lean body mass (LBM)** is an example of a model available with current devices.

TCI can be used for induction and maintenance of ASA I and II adult patients in general and cardiac anaesthesia. There are insufficient data to make recommendations for delivery of Ultiva by TCI for ASA III and IV patients, spontaneous ventilation anaesthesia, use in ICU sedation, monitored conscious sedation or in children.

For TCI in adults the recommended dilution of Ultiva is 20 to 50 micrograms/mL.

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

1. General Anaesthesia:

1.1 Dosage in Adults

Administration by Manually-Controlled Infusion

The following table summarises the starting infusion rates and dose range for various anaesthetic situations:

Table 4: DOSING GUIDELINES FOR ADULTS

INDICATION	Ultiva	Ultiva Continuous Infusion	
	Slow Bolus Injection (µg/kg)	Starting Rate (µg/kg/min)	Range (µg/kg/min)
Induction of anaesthesia	1 (administer over 60 seconds)*	0.5 to 1	-
Maintenance of anaesthesia e.g. with any one of:			
Nitrous oxide (66%)		0.4	0.1 to 2
Isoflurane (Starting dose 0.5 MAC)	0.5-1	0.25	0.05 to 2
Propofol (Starting dose 100 µg/kg/min)		0.25	0.05 to 2

MAC = minimum alveolar concentration

*** When given by bolus infusion AT INDUCTION, Ultiva should be administered over 60 seconds (see PRECAUTIONS: Muscle Rigidity).**

(See **INSTRUCTIONS FOR USE** for additional information, including tables to help titrate Ultiva to the patient's anaesthetic needs.)

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**).

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 **(see PRECAUTIONS: Muscle rigidity - prevention and management)**. Ultiva can be administered at an infusion rate of 0.5 to 1 µg/kg/min with or without an **initial bolus infusion of 1 µg/kg over 60 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 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 µ-opioid response. In response to light anaesthesia, supplemental bolus infusions may be administered every 2 to 5 minutes.

Analgesia

On cessation of infusion, Ultiva has a short-lasting analgesic effect. Post-operative pain management should be considered and, where appropriate, begun prior to the termination of Ultiva infusion.

Guidelines for discontinuation

Upon discontinuation of Ultiva the intravenous tubing should be cleared to prevent the inadvertent administration of Ultiva at a later point in time (see **PRECAUTIONS**). Due to the 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 generally anticipated, alternative 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 follow-up care.

Concomitant medication

Ultiva decreases the dose of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

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.

Administration by Target-Controlled Infusion

Induction and maintenance of anaesthesia in ventilated patients: Ultiva TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 4). In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanil concentrations ranging from 3 to 8 ng/mL. Ultiva should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 ng/mL may be required.

As with manually-controlled infusion, 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 Table 4).

There are insufficient data to make recommendations on the use of TCI for spontaneous ventilation anaesthesia.

Guidelines for discontinuation/continuation into the immediate post-operative period: At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (*see **Guidelines for discontinuation*** under ***DOSAGE and ADMINISTRATION - General Anaesthesia – Dosage in Adults – Administration by Manually-Controlled Infusion*).**

There are insufficient data to make recommendations on the use of TCI for the management of post-operative analgesia.

1.2 Dosage in Paediatric patients (1-12 years of age)

Administration by Manually-Controlled Infusion

Induction of anaesthesia:

There are insufficient data to make a dosage recommendation.

Maintenance of anaesthesia:

Table 5: DOSING GUIDELINES FOR MAINTENANCE OF ANAESTHESIA IN PAEDIATRIC PATIENTS (1-12 years of age)

*Concomitant Anaesthetic Agent	Ultiva Bolus Injection (Optional) (μg/kg)	Ultiva Continuous Infusion (μg/kg/min)	
		Starting Rate	Typical Maintenance Rates
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

*co-administered 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. 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 in 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 in Adults - Guidelines for discontinuation**).

Administration by Target-Controlled Infusion

Ultiva TCI has not been studied in paediatric patients.

Paediatric patients aged less than 1 year:

The pharmacokinetic profile of remifentanil in paediatric patients aged more than 2 months is comparable to that seen in adults after correction for body weight differences. However, there are insufficient pharmacokinetic and clinical data to make dosage recommendations for patients aged less than 1 year.

2. Cardiac Anaesthesia:

2.1 Dosage in Adults

Administration by Manually-Controlled Infusion

Table 6: DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

Indication	Ultiva Bolus Injection (μg/kg)	Ultiva Continuous Infusion (μg/kg/min)	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	–
Maintenance of anaesthesia			
Isoflurane (starting dose 0.4 MAC)	0.5 to 1	1	0.003 to 4

Propofol (starting dose 50μg/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 1μg/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 6 minutes after the start of infusion in order to minimise the response to intubation.

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 0.5μg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see **PHARMACOLOGY - Cardiac anaesthesia**).

Concomitant medication: At the doses recommended above, Ultiva significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with Ultiva (see **General Anaesthesia: Dosage in 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 rate adjusted to meet the individual patient's requirements.

Guidelines for discontinuation: Ultiva should only be continued as an analgesic in the immediate post-operative period, and subsequently discontinued during transition to longer acting analgesia, in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by medically qualified 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 intubation, and assisted ventilation.

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 in Adults - Guidelines for discontinuation**).

It is recommended that the Ultiva infusion is discontinued by reducing the infusion rate by 25% decrements in at least 10 minute intervals until the infusion is discontinued. During

weaning from the ventilator the Ultiva infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

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

Administration by Target-Controlled Infusion

There are insufficient data to make recommendations for delivery of Ultiva by TCI for ASA III and IV patients undergoing cardiac surgery.

There are insufficient data to make recommendations on the use of TCI for the management of post-operative analgesia.

Induction and maintenance of anaesthesia: Ultiva TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table 6). In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 ng/mL have been used in clinical studies. At the doses recommended above, remifentanil 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 Table 6).

Guidelines for discontinuation / continuation into the immediate post-operative period: At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see **Guidelines for discontinuation** under **Dosage and Administration - Cardiac Anaesthesia – Dosage in Adults – Administration by Manually-Controlled Infusion).**

2.2 Dosage in Paediatric patients

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

3. Special patient populations:

3.1 Dosage in Elderly Patients (over 65 years of age)

(a) 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.

(b) Cardiac anaesthesia: No initial dose reduction is required (see **Cardiac anaesthesia – Dosing Guidelines for Cardiac Anaesthesia**).

Administration by Manually-Controlled Infusion

Intensive care: No initial dose reduction is required **(see DOSAGE and ADMINISTRATION, Use in Intensive Care).**

Administration by Target-Controlled Infusion

General anaesthesia: Because of the increased sensitivity of elderly patients to remifentanil, when administering Ultiva by TCI in this population the initial target concentration should be 1.5 to 4 ng/mL with subsequent titration to response.

3.2 Dosage in Obese Patients

Administration by Manually-Controlled Infusion

For manually controlled infusion, 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.

Administration by Target-Controlled Infusion

With the calculation of lean body mass (LBM) used in the Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m2 and in male patients with BMI greater than 40 kg/m2. To avoid underdosing in these patients, Ultiva TCI should be titrated carefully to individual response.

3.3 Dosage in Patients with Renal Impairment

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

3.4 Dosage in Patients with Hepatic Impairment

No adjustment of the initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of Ultiva is unchanged in this patient population. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of Ultiva. These patients should be closely monitored and the dose of Ultiva titrated to individual patient needs.

3.5 Neurosurgery

There is limited clinical experience with patients undergoing neurosurgery.

3.6 ASA III/IV patients

(a) 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.

Manually Controlled Infusion: **Initial dosage reduction and subsequent titration to effect is therefore recommended.**

Target-Controlled Infusion**: TCI is not recommended for ASA III or IV patients.**

(b) **Cardiac anaesthesia:** No initial dose reduction is required (see **Cardiac Anaesthesia – Dosing Guidelines for Cardiac Anaesthesia**).

(c) **Intensive Care:** No initial dose reduction is required (see **Use in Intensive Care**).

3.7 Use in Intensive Care

Administration by Manually Controlled Infusion

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 0.1µg/kg/min to 0.15µg/kg/min. The infusion rate should be titrated in increments of 0.025µg/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 0.2µg/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 0.025µg/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 three days (see **CLINICAL TRIALS – Intensive Care Unit**).

Table 7 summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients:-

Table 7: DOSING GUIDELINES FOR USE OF ULTIVA WITHIN THE INTENSIVE CARE SETTING

CONTINUOUS INFUSION microgram/kg/min	
Starting Rate	**Maintenance Range***
0.1 to 0.15	0.006 to 0.74

* Range of doses used in clinical trials to maintain adequate analgesia and sedation.

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 in Table 8.

Table 8: 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 administered as an admixture.

Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the existing Ultiva infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that an Ultiva infusion rate of at least 0.1mcg/kg/min should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25%-50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25microgram/kg/min, maximum 0.75microgram/kg/min, has been administered for provision of additional anaesthesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of Ultiva: Due to the very rapid offset of action of Ultiva, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents at a sufficient time in advance to allow the therapeutic effects of these agents to become established. The range of options for analgesia includes long acting oral, intravenous, or regional analgesics controlled by the nurse of the patient. These techniques should always be titrated to individual patient need as the infusion of Ultiva is reduced (see below). It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to 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 down in stages to 0.1mcg/kg/min over a period up to 1 hour prior to extubation.

Following extubation, the infusion rate should be reduced by 25% decrements in at least 10-minute intervals until the infusion is discontinued. During weaning from the ventilator the Ultiva infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Paediatric Intensive Care Patients – There are no data available on use in paediatric patients.

Renally-impaired intensive care patients - No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy.

Recovery following discontinuation of a remifentanil infusion may be slightly prolonged in moderate to severe renal impairment (see **PHARMACOLOGY/PHARMACOKINETICS** - **Pharmacokinetics in patients with renal impairment**).

Administration by Target-Controlled Infusion

Ultiva TCI has not been studied in intensive care patients.

INSTRUCTIONS FOR USE:

Reconstitution and Dilution

To reconstitute the powder, add 1 mL of diluent (see **Physical Compatibilities** for recommended diluents) per mg of remifentanil. Shake well to dissolve. When reconstituted as directed, the solution contains approximately 1 mg of remifentanil activity per 1 mL. ULTIVA should be diluted to a final concentration of 20, 25, 50, or 250 μg/mL prior to administration (see Table 9).

50 μg/mL is the recommended dilution for adults and 20-25 μg/mL for paediatric patients aged 1 year and over. The dilution is dependent upon the technical capability of the infusion device and the expected requirements of the patient. Ultiva should not be administered without dilution.

Table 9: Reconstitution and Dilution of Ultiva

Final Concentration	Amount of Ultiva In each vial	Final volume after Reconstitution and dilution
20 μg/mL	1 mg 2 mg 5 mg	50 mL 100 mL 250 mL
25 μg/mL	1 mg 2 mg 5 mg	40 mL 80 mL 200 mL
50 μg/mL	1 mg 2 mg 5 mg	20 mL 40 mL 100 mL
250 μg/mL	5 mg	20 mL

Physical Compatibilities

Ultiva is chemically and physically stable and should be used within 24 hours of preparation and storage at 2-8°C, after reconstitution and further dilution to concentrations of 20 to 250 µg/mL with one of the following recommended intravenous fluids:

Sterile Water for Injection

5% Glucose Injection

5% Glucose and 0.9% Sodium Chloride Injection

0.9% Sodium Chloride Injection

0.45% Sodium Chloride Injection

Ultiva contains no antimicrobial preservative and care must be taken to assure the sterility of prepared solutions. Reconstituted product should be used promptly and any unused material discarded. If storage is necessary, hold at 2-8°C for not more than 24 hours to reduce microbiological hazard.

(See also **Physical Incompatibilities**)

Ultiva has been shown to be compatible with the following intravenous fluids when administered **into a running intravenous line**:

Lactated Ringer's Injection

Lactated Ringer's and 5% Glucose Injection

Ultiva has been shown to be compatible with propofol when administered into a running intravenous line.

Physical Incompatibilities

Continuous infusions of Ultiva must be administered by a calibrated infusion device, where possible via a dedicated intravenous line, otherwise into a fast flowing IV line.

Ultiva should only be admixed with those infusion solutions recommended (see also **Physical Compatibilities**).

Ultiva should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Glucose Injection.

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

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

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

Administration by Manually-Controlled Infusion

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).

The following tables give guidelines for infusion rates of Ultiva for manually-controlled infusion:

Table 10 Ultiva for Injection Infusion Rates (mL/kg/h)

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/h)			
	20 µg/mL 1 mg/50 mL	25 µg/mL 1 mg/40 mL	50 µg/mL 1 mg/20 mL	250 µg/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 11 Ultiva for Injection Infusion Rates (mL/h) for a 20µg/mL Solution

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

0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 12 Ultiva for Injection Infusion Rates (mL/h) for a 25 µg/mL Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	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 13 Ultiva for Injection Infusion Rates (mL/h) for a 50 µg/mL Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)							
	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 14 Ultiva for Injection Infusion Rates (mL/h) for a 250 µg/mL Solution

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

Administration by Target-Controlled Infusion

For TCI the recommended dilution of Ultiva is 20 to 50 micrograms/mL.

The following table gives guidelines for blood concentrations achieved at steady steady state with MCI in a 70 kg, 170 cm, 40 year old, male patient (using Minto PK model).

Table 15: Blood concentrations achieved at steady state with MCI in a 70 kg, 170 cm, 40 year old, male patient (using Minto PK model)

Remifentanil Infusion Rate (µg/kg/min)	Remifentanil blood concentration (ng/mL)
0.05	1.3
0.10	2.6
0.25	6.3
0.40	10.4
0.50	12.6
1.0	25.2
2.0	50.5

Discontinuation:

Upon discontinuation of Ultiva sufficient drug may remain in intravenous lines or in the dead space of cannulae to cause opioid-related effects (e.g. respiratory depression) if

the line is flushed. Therefore, appropriate measures should be taken to avoid such inadvertent administration of Ultiva (see **PRECAUTIONS**)**.**

OVERDOSAGE:

Overdosage is manifested by an extension of the pharmacologically predictable actions of Ultiva.

In the event of overdosage or suspected overdosage, 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 agents for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of naloxone may be given as a specific antidote to manage severe respiratory depression and muscle rigidity.

PRESENTATION AND STORAGE CONDITIONS:

Ultiva Injection is a sterile, non-pyrogenic, preservative-free, white to off-white lyophilised powder for intravenous use and is available as:

1 mg remifentanil base (as the hydrochloride salt) in 3 mL vials in cartons of 5.

2 mg remifentanil base (as the hydrochloride salt) in 5 mL vials in cartons of 5.

5 mg remifentanil base (as the hydrochloride salt) in 10 mL vials in cartons of 5.

Container labelled “Single dose.”

Store below 25°C.

The reconstituted solution is chemically and physically stable for 48 hours at room temperature but since the product includes no preservative, reconstituted product should be used promptly and any unused material discarded. If storage is necessary, hold at 2-8°C for not more than 24 hours to reduce microbiological hazard.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street

Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 8. Controlled Drug

Attachment 1: Product information for AusPAR Ultiva GlaxoSmithKline Australia Pty Ltd PM-2011-00909-3-1 Final 29 January 2013. This Product Information was approved at the time this AusPAR was published.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 4 May 1998

Attachment 1: Product information for AusPAR Ultiva GlaxoSmithKline Australia Pty Ltd PM-2011-00909-3-1 Final 29 January 2013. This Product Information was approved at the time this AusPAR was published.

DATE OF MOST RECENT AMENDMENT: 28 June 2012

Version 4.0

Ultiva® is a registered trade mark of the GlaxoSmithKline group of companies.