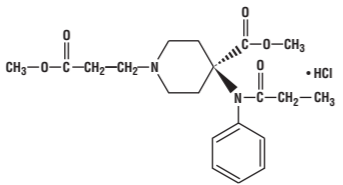


DESCRIPTION

ULTIVA (remifentanyl hydrochloride) for Injection is a μ -opioid agonist chemically designated as a 3-(4-methoxyphenyl)-4-(1-(oxopropylphenyl)-1-piperidinyl)propanoic acid methyl ester, hydrochloride salt, $C_{20}H_{28}N_2O_5\cdot HCl$, with a molecular weight of 412.31. It has the following chemical structure:



ULTIVA is a sterile, nonpyrogenic, preservative-free, white to off-white lyophilized powder for intravenous (IV) administration after reconstitution. Each vial contains 1, 2, or 5 mg remifentanyl base, 15 mg glycine, and hydrochloric acid to buffer the solutions to a nominal pH of 3 after reconstitution. When reconstituted as directed, solutions of ULTIVA are clear and colorless and contain remifentanyl hydrochloride (HCl) equivalent to 1 mg/mL of remifentanyl base. The pH of reconstituted solutions of ULTIVA ranges from 2.5 to 3.5. Remifentanyl HCl has a pKa of 7.07. Remifentanyl HCl has an n-octanol-water partition coefficient of 17.9 at pH 7.3.

CLINICAL PHARMACOLOGY

ULTIVA is a μ -opioid agonist with rapid onset and peak effect, and short duration of action. The μ -opioid activity of ULTIVA is antagonized by opioid antagonists such as naloxone.

Unlike other opioids, ULTIVA is rapidly metabolized by hydrolysis of the propanoic acid-methyl ester linkage by nonspecific blood and tissue esterases. ULTIVA is not a substrate for plasma cholinesterase (pseudocholinesterase) and, therefore, patients with atypical cholinesterase are expected to have normal duration of action.

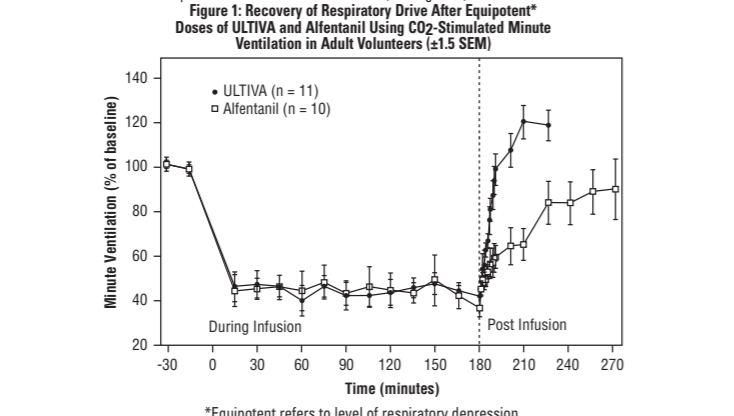
Pharmacodynamics: The analgesic effects of ULTIVA are rapid in onset and offset. Its effects and side effects are dose dependent and similar to other μ -opioids. ULTIVA in humans has a rapid blood-brain equilibrium half-time of 1 ± 1 minutes (mean \pm SD) and a rapid onset of action. The pharmacodynamic effects of ULTIVA 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 administration. Recovery from the effects of ULTIVA 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 anesthetic technique, ULTIVA can be rapidly titrated to the desired depth of anesthesia/analgesia (e.g., as required by varying levels of intraoperative stress) by changing the continuous infusion rate or by administering an IV bolus injection.

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

Respiration: ULTIVA depresses respiration in a dose-related fashion. Unlike other fentanyl analogs, the duration of action of ULTIVA at a given dose does not increase with increasing duration of administration, due to lack of drug accumulation.

ULTIVA has an equal level of respiratory depression and respiratory recovery of respiratory drive after 3-hour infusions was more rapid and less variable with ULTIVA (see Figure 1).

Figure 1: Recovery of Respiratory Drive After Equipotent* Doses of ULTIVA and Alfentanil Using CO₂-Stimulated Minute Ventilation in Adult Volunteers (± 1.5 SEM)



*Equipotent refers to level of respiratory depression.

Spontaneous respiration occurs at blood concentrations of 4 to 5 ng/mL in the absence of other anesthetic agents; for example, after discontinuation of a 0.25-mcg/kg/min infusion of remifentanyl, these blood concentrations would be reached in 2 to 4 minutes. In patients undergoing general anesthesia, the rate of respiratory recovery depends upon the concurrent anesthetic. N_2O < propofol < isoflurane (see CLINICAL TRIALS: Recovery).

Muscle Rigidity: Skeletal muscle rigidity can be caused by ULTIVA and is related to the dose and speed of administration. ULTIVA may cause chest wall rigidity (inability to ventilate) after single doses of >1 mcg/kg administered over 30 to 60 seconds or infusion rates >0.1 mcg/kg/min; peripheral muscle rigidity may occur at lower doses. Administration of doses <1 mcg/kg may cause chest wall rigidity when given concurrently with a continuous infusion of ULTIVA. Prior or concurrent administration of a neuromuscular blocking agent may attenuate the development of muscle rigidity. Excessive muscle rigidity can be treated by decreasing the rate or discontinuing the infusion of ULTIVA or by administering a neuromuscular blocking agent.

Histamine Release: Assays of histamine in patients and normal volunteers have shown no elevation in plasma histamine levels after administration of ULTIVA in doses up to 30 mcg/kg over 60 seconds.

Analgesic Efficacy: In a randomized, double-blind, controlled study, supplemental doses of 0.5 to 1 mcg/kg, incremental increases in infusion rate >0.05 mcg/kg/min, and blood concentrations exceeding 5 ng/mL (typically produced by infusions of 0.2 mcg/kg/min) have been associated with transient and reversible respiratory depression, apnea, and muscle rigidity.

Anesthesia: ULTIVA is synergistic with the activity of hypnotics (propofol and thiopental), inhaled anesthetics, and benzodiazepines (see CLINICAL TRIALS: PRE-INDUCTION, and DOSAGE AND ADMINISTRATION).

Age: The pharmacodynamic activity of ULTIVA (as measured by the ECG) for development of Δ (delta waves on the EEG) increases with increasing age. The ECG of remifentanyl for this measure was 50% less in patients over 65 years of age when compared to healthy volunteers (25 years of age) (see DOSAGE AND ADMINISTRATION).

Gender: No differences have been shown in the pharmacodynamic activity (as measured by the EEG) of ULTIVA between men and women.

Drug Interaction: In animals the duration of muscle paralysis from succinylcholine is not prolonged by remifentanyl.

Intraocular Pressure: There was no change in intraocular pressure after the administration of ULTIVA prior to ophthalmic surgery under monitored anesthesia care.

Cerebrodynamics: Under isoflurane-nitrous oxide anesthesia (PacO₂ <30 mmHg), a 1-minute infusion of ULTIVA (0.5 or 1.0 mcg/kg) produced no change in intracranial pressure. Mean arterial pressure and cerebral perfusion decreased as expected with increasing concentrations of isoflurane and nitrous oxide. Cerebral blood flow reactivity to carbon dioxide remained intact. In humans, no epileptiform activity was seen on the EEG (n = 44) at remifentanyl doses up to 8 mcg/kg/min.

Renal Dysfunction: The pharmacodynamics of ULTIVA (ventilatory response to hypercarbia) are unaltered in patients with end stage renal disease (creatinine clearance <10 mL/min).

Hepatic Impairment: The pharmacodynamics of ULTIVA (ventilatory response to hypercarbia) are unaltered in patients with severe hepatic dysfunction awaiting liver transplant.

Pharmacokinetics: After IV doses administered over 60 seconds, the pharmacokinetics of remifentanyl fit a three-compartment model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes. Since the terminal elimination component contributes less than 10% of the overall area under the curve, the terminal half-life of ULTIVA is 3 to 10 minutes. This is similar to the 3- to 10-minute half-life measured after termination of prolonged infusions (up to 4 hours; see Figure 2) and correlates with recovery times observed in the clinical setting after infusions up to 12 hours. Concentrations of remifentanyl are proportional to the dose administered throughout the recommended dose range. The pharmacokinetics of remifentanyl are unaffected by the presence of renal or hepatic impairment.

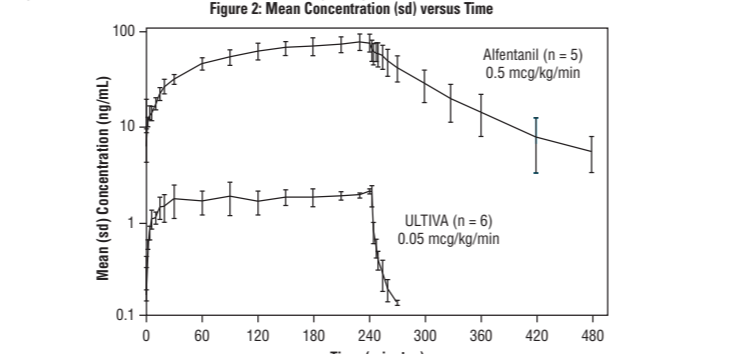
Distribution Volume: The distribution volume of remifentanyl is approximately 100 mL/kg and represents distribution throughout the blood and rapidly perfused tissues. Remifentanyl subsequently distributes into peripheral tissues with a steady-state volume of distribution of approximately 350 mL/kg. These two distribution volumes generally correlate with total body weight (except in severely obese patients when they correlate better with ideal body weight [IBW]). Remifentanyl is approximately 70% bound to plasma proteins of which two-thirds is binding to albumin- α 1-acid-glycoprotein.

Metabolism: Remifentanyl is an esterase-metabolized opioid. A labile ester linkage renders this compound susceptible to hydrolysis by nonspecific esterases in blood and tissues. This hydrolysis results in the production of the carboxylic acid metabolite (3-(4-methoxycarbonyl-4-(1-(oxopropylphenylamino)-1-piperidinyl)propanoic acid), and represents the principal metabolic pathway for remifentanyl (>95%). The carboxylic acid metabolite is essentially inactive (1/4000 as potent as the parent drug) and is excreted by the kidneys with a half-life of approximately 80 minutes. Remifentanyl is not metabolized by plasma cholinesterase (pseudocholinesterase) and is not appreciably metabolized by the liver or lung.

Elimination: The clearance of remifentanyl in young, healthy adults is approximately 40 mL/min/kg. Clearance generally correlates with total body weight (except in severely obese patients when it correlates better with IBW). The high

clearance of remifentanyl combined with a relatively small volume of distribution produces a short elimination half-life of approximately 3 to 10 minutes (see Figure 2). This value is consistent with the time taken for blood or effect site concentrations to fall by 50% (context-sensitive half-time) which is approximately 3 to 6 minutes. Unlike other fentanyl analogs, the duration of action does not increase with prolonged administration.

Figure 2: Mean Concentration (sd) versus Time



Titration to Effect: The rapid elimination of remifentanyl permits the titration of infusion rate without concern for prolonged duration. In general, every 0.1 mcg/kg/min change in IV infusion rate will lead to a corresponding 2.5-ng/mL change in blood concentration within 5 to 10 minutes. Effects of remifentanyl on patients only a more rapid increase (within 3 to 5 minutes) to a new steady state can be achieved with a 1.0-mcg/kg bolus dose in conjunction with an infusion rate increase.

Special Populations: Pediatrics: In pediatric patients, 5 days to 17 years of age (n = 47), the clearance and volume of distribution of remifentanyl were increased in younger children and declined to young healthy adult values by age 17. The technique (n = 86) in children 1 to 12 years of age was approximately 30.5 \pm 36.8 mL/min/kg (mean \pm SD) while in adolescents (13 to 16 years) this value was 57.2 \pm 21.1 mL/min/kg. The total (steady-state) volume of distribution in neonates was 452 \pm 144 mL/kg versus 233 \pm 30.6 mL/kg in adolescents. The half-life of remifentanyl was the same in neonates and adolescents. Clearance of remifentanyl was maintained at or above normal adult values in patients 5 days to 17 years of age.

Renal Impairment: The pharmacokinetic profile of ULTIVA is not changed in patients with end stage renal disease (creatinine clearance <10 mL/min). In anephric patients, the half-life of the carboxylic acid metabolite increases from 30 minutes to 30 hours. The metabolite is removed by hemodialysis with a dialysis extraction ratio of approximately 30%.

Hepatic Impairment: The pharmacokinetics of remifentanyl and its carboxylic acid metabolite are unchanged in patients with severe hepatic impairment.

Elderly: The clearance of remifentanyl is reduced (approximately 25%) in the elderly (>65 years of age) compared to young adults (average 25 years of age). However, remifentanyl blood concentrations fall as rapidly after termination of administration in the elderly as in young adults.

Gender: There is no significant difference in the pharmacokinetics of remifentanyl in male and female patients after correcting for differences in weight.

Obesity: There is no difference in the pharmacokinetics of remifentanyl in non-obese versus obese (greater than 30% over IBW) patients when normalized to IBW.

Cardiopulmonary Bypass: Remifentanyl clearance is reduced by approximately 20% during hypothermic CPB.

Drug Interactions: Remifentanyl clearance is not altered by concomitant administration of thiopental, isoflurane, propofol, or remifentanyl during anesthesia. *In vitro* studies with atracurium, mivacurium, esmolol, echiolophthal, metoprolol, physostigmine, and midazolam revealed no inhibition of remifentanyl hydrolysis in whole human blood by these drugs.

CLINICAL TRIALS

ULTIVA was evaluated in 3341 patients undergoing general anesthesia (n = 2706) and monitored anesthesia care (n = 639). These patients were evaluated in the following settings: inpatient (n = 2079) which included cardiovascular (n = 426), and ambulatory (n = 653) patients (n = 1340). Four-hundred and eighty-six (486) elderly patients (age range 66 to 90 years) and 410 pediatric patients (age range birth to 12 years) received ULTIVA. Of the general anesthesia patients, 682 also received ULTIVA as an IV analgesic agent during the immediate postoperative period.

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

Induction of Anesthesia: ULTIVA was administered with isoflurane, propofol, or thiopental for the induction of anesthesia (n = 1362). The majority of patients (80%) received propofol as the concurrent agent. ULTIVA reduced the propofol induction dose of ULTIVA by 25% 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 anesthesia; however, it should not be used as a sole agent because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and tachycardia. The addition of a small dose of propofol or thiopental to ULTIVA for the induction of anesthesia resulted in a rapid or concurrently with ULTIVA during the induction of anesthesia markedly decreased the incidence of muscle rigidity from 20% to <1%.

Coronary Artery Bypass Surgery: ULTIVA was originally administered to 225 patients with patent left ventricular CABG surgery in two dose-ranging studies without active comparators. Subsequently, two double-blind, double-dummy clinical studies (N = 426) evaluated ULTIVA (n = 236) at recommended doses versus active comparators (n = 190).

The first comparator study, a multi-center, randomized, double-blind, double-dummy, parallel-group study (N = 369), compared ULTIVA (n = 201) with fentanyl (n = 168) in adult patients undergoing elective CABG surgery. Subjects received 1 to 3 mg midazolam and 0.05-mcg/kg morphine IV as premedication. Anesthesia was induced with propofol 0.5 mcg/kg (higher doses administered with ULTIVA were associated with excessive hypotension) over one minute plus 10-mg boluses every 10 seconds until loss of consciousness followed by either cisatracurium 0.2 mcg/kg or vecuronium 0.15 mcg/kg. Patients randomized to ULTIVA received a 1 mcg/kg/min infusion of ULTIVA followed by a placebo bolus administered over 3 minutes. In the active control group, a placebo IV infusion was started and a fentanyl bolus administered over 3 minutes. All subjects received isoflurane 0.5% and nitrous oxide 50% during the procedure. The incidence of hypotension was 0.5% during maintenance of the group randomized to ULTIVA versus as needed 0.5-1 mcg/kg/min IV rate increases (to a maximum of 4 mcg/kg/min) of ULTIVA and 1 mcg/kg IV boluses of ULTIVA. The active control group received 2 mcg/kg IV boluses of fentanyl and increases in placebo IV infusion rate.

The second comparator study, a multi-center, double-blind, randomized, parallel group study (N = 57), compared ULTIVA (n = 35) to fentanyl (n = 22) in adult patients randomized to CABG surgery with patent left ventricular CABG surgery (ejection fraction <0.35). Subjects received oral lorazepam 40 mcg/kg as premedication. Anesthesia was induced using etomidate until loss of consciousness, followed by a low-dose propofol infusion (3 mcg/kg/hr) and pancuronium 0.15 mcg/kg. Subjects in the group administered ULTIVA received a placebo bolus dose and a continuous infusion of ULTIVA 1 mcg/kg/min and subjects in the fentanyl group received a bolus loading dose of 15 mcg/kg and placebo continuous infusion. During maintenance, supplemental boluses of ULTIVA were administered as needed. The maximum increase in the fentanyl group was 4 mcg/kg/min. ULTIVA were administered to one group; propofol was administered to the other. The study group was given intermittent maintenance bolus doses of 2 mcg/kg and increases in the placebo infusion rate.

In these two studies, using a high dose opioid technique with ULTIVA as a component of a balanced or total intravenous anesthetic regimen, the remifentanyl regimen effectively attenuated response to maximal thermal spread generally better than the fentanyl regimen. In both studies, the active control (fentanyl). While this provides evidence for the efficacy of remifentanyl as an analgesic, this setting of use must be interpreted with caution since these results as evidence of superiority of remifentanyl over the active control, since these studies did not make any attempt to evaluate and compare the optimal analgesic doses of either drug in this setting.

Neurosurgery: ULTIVA was administered to 61 patients undergoing craniotomy for removal of a supratentorial mass lesion. 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 after craniotomy was 5 minutes (range 1 to 19 minutes). Intracranial pressure and cerebrovascular responsiveness to carbon dioxide were normal (see CLINICAL PHARMACOLOGY).

A randomized, controlled study compared ULTIVA (n = 31) to fentanyl (n = 32). ULTIVA (1 mcg/kg/min) and fentanyl (2 mcg/kg/min) were administered after induction with thiopental and pancuronium. A similar number of patients (6%) received ULTIVA and fentanyl had hypotension during induction. ULTIVA was administered to one group; propofol was administered to the other. The study group was given intermittent maintenance bolus doses of 2 mcg/kg and increases in the placebo infusion rate of 0.4 mcg/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 anesthesia, whereas fentanyl was discontinued at the time of bone flap replacement (a median time of 44 minutes before the end of surgery). The median time to extubation was 5 minutes (range 1 to 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 (28%) 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 patients receiving fentanyl (median 25 versus 35 minutes, respectively, P = 0.04). No adverse cerebrovascular effects were seen in this study (see CLINICAL PHARMACOLOGY).

Continuation of Analgesic Use into the Immediate Postoperative Period: Analgesia with ULTIVA in the immediate postoperative period (until approximately 30 minutes after extubation) was studied in 401 patients in four dose-finding studies and in 281 patients in two efficacy studies. In the dose-finding studies, the use of bolus doses of ULTIVA and incremental infusion rate increases >0.05 mcg/kg/min resulted in a higher incidence of hypotension compared to ULTIVA to treat postoperative pain are not recommended and incremental infusion rate increases should not exceed 0.025 mcg/kg/min at 5-minute intervals.

In two efficacy studies, ULTIVA 0.1 mcg/kg/min was started immediately after discontinuing anesthesia. Incremental infusion rate increases of 0.025 mcg/kg/min every 5 minutes were given to treat moderate to severe postoperative pain. In Study 1, 50% decreases in infusion rate were made and respiratory rate decreased below 12 breaths/min. In Study 2, the same decreases were made but respiratory rate was below 8 breaths/min. With this difference in criteria for infusion rate decrease, the incidence of respiratory depression was lower in Study 1 (4%) than in Study 2 (12%). In both studies, ULTIVA provided effective analgesia (no or mild pain with respiratory rate >8 breaths/min) in approximately 60% of patients at mean final infusion rates of 0.1 to 0.125 mcg/kg/min.

Study 2 was a double-blind, randomized, controlled study in which patients received either morphine sulfate 0.15 mcg/kg administered 20 minutes before the anticipated end of surgery plus 2-mg bolus doses for supplemental analgesia) or ULTIVA (as described above). Emergence from anesthesia was similar between groups; median time to extubation was 5 to 6 minutes for both. ULTIVA provided effective analgesia in 58% of patients compared to 33% of patients receiving morphine. Respiratory depression occurred in 12% of patients receiving ULTIVA compared to 4% of morphine patients. For patients who received ULTIVA, morphine sulfate 0.15 mcg/kg was administered 5 to 10 minutes before discontinuing ULTIVA. Within 30 minutes after discontinuation of ULTIVA, the percentage of patients with effective analgesia decreased to 34%.

Monitored Anesthesia Care: ULTIVA has been studied in the monitored anesthesia care setting in 609 patients in eight clinical trials. Nearly all patients received supplemental oxygen in these studies. Two early dose-finding studies

to doubling the rate to 0.5 mcg/kg approximately 5 minutes before the start of the major surgical stress event. Doubling the rate decreased the incidence of signs of light anesthesia 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 2169 patients receiving ULTIVA for periods up to 16 hours, recovery from anesthesia 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 anesthesia and 10 minutes (range: <3 to 17 minutes) in inpatient anesthesia. Recovery of spontaneous breathing after propofol or propofol was faster than in those using isoflurane as the concurrent anesthetic. There was no case of remifentanyl-induced delayed respiratory depression occurring more than 30 minutes after discontinuation of remifentanyl (see PRECAUTIONS).

In a double-blind, randomized study, administration of morphine sulfate (0.15 mcg/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 remifentanyl-propofol total IV anesthesia.

Spontaneous Ventilation Anesthesia: Two randomized, dose-ranging studies (n = 127) examined the administration of ULTIVA to outpatients undergoing general anesthesia with a laryngeal mask. Starting infusion rates of ULTIVA of 0.05 mcg/kg/min provided supplemental analgesia while allowing spontaneous ventilation with propofol or isoflurane.

Bolus doses of ULTIVA during spontaneous ventilation lead to transient periods of apnea, respiratory depression, and chest wall rigidity. ULTIVA was administered to 136 patients in 13 studies. In 10 studies, ULTIVA was administered to patients undergoing general anesthesia with a laryngeal mask. Recovery of spontaneous breathing after propofol or propofol was faster than in those using isoflurane as the concurrent anesthetic. There was no case of remifentanyl-induced delayed respiratory depression occurring more than 30 minutes after discontinuation of remifentanyl (see PRECAUTIONS).

In a randomized, double-blind study, ULTIVA with or without midazolam was evaluated in 159 patients undergoing superficial surgical procedures under local anesthesia. ULTIVA was administered without midazolam as a 1-mcg/kg dose over 30 seconds followed by a continuous infusion of 0.1 mcg/kg/min. In the group of patients that received midazolam, propofol was administered as a bolus 30 seconds before the start of the procedure. ULTIVA was administered to one group; propofol was administered to the other. The study group was given intermittent maintenance bolus doses of 2 mcg/kg and increases in the placebo infusion rate of 0.4 mcg/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 anesthesia, whereas fentanyl was discontinued at the time of bone flap replacement (a median time of 44 minutes before the end of surgery). The median time to extubation was 5 minutes (range 1 to 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 (28%) 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 patients receiving fentanyl (median 25 versus 35 minutes, respectively, P = 0.04). No adverse cerebrovascular effects were seen in this study (see CLINICAL PHARMACOLOGY).

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demonstrated that use of sedation as an endpoint for titration of ULTIVA led to a high incidence of muscle rigidity (69%) and respiratory depression. Subsequent trials titrated ULTIVA to specific clinical endpoints of patient comfort, analgesia, and adequate respiratory depression and other effects may occur in newborns whose mothers are given ULTIVA shortly before delivery. The safety of ULTIVA during labor or delivery has not been demonstrated. Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanyl and its metabolites. In a human clinical trial, the average maternal remifentanyl concentrations were approximately twice those seen in the fetus. In some cases, however, fetal concentrations were similar to those in the mother. The umbilical arteriovenous ratio of remifentanyl concentrations was approximately 30% suggesting metabolic clearance of remifentanyl in the neonate.

Nursing Mothers: It is not known whether remifentanyl is excreted in human milk. After receiving radioactive-labeled remifentanyl, the radioactivity was present in the milk of lactating rats. Because fentanyl analogs are excreted in human milk, caution should be exercised when ULTIVA is administered to a nursing woman.

ADVERSE EVENTS
ULTIVA produces adverse events that are characteristic of μ -opioids, such as respiratory depression, bradycardia, hypotension, and skeletal muscle rigidity. These adverse events dissipate within minutes of discontinuing or decreasing the infusion rate of ULTIVA. See CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS on the management of these events.

Adverse event information is derived from controlled clinical trials that were conducted in a variety of surgical procedures of varying duration, using a variety of premedications and other anesthetics, and in patient populations with diverse characteristics including underlying disease.

Adults: Approximately 2770 adult patients were exposed to ULTIVA in controlled clinical trials. The frequencies of adverse events during general anesthesia with the recommended doses of ULTIVA are given in Table 3. Each patient was counted once for each type of adverse event.

hind limb dysfunction, and incoordination. These effects are believed to be caused by the glycine. Glycine is a commonly used excipient in IV products and this finding has no relevance for IV administration of ULTIVA.

Labor and Delivery: Respiratory depression and other adverse effects may occur in newborns whose mothers are given ULTIVA shortly before delivery. The safety of ULTIVA during labor or delivery has not been demonstrated. Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanyl and its metabolites. In a human clinical trial, the average maternal remifentanyl concentrations were approximately twice those seen in the fetus. In some cases, however, fetal concentrations were similar to those in the mother. The umbilical arteriovenous ratio of remifentanyl concentrations was approximately 30% suggesting metabolic clearance of remifentanyl in the neonate.

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Adverse event information is derived from controlled clinical trials that were conducted in a variety of surgical procedures of varying duration, using a variety of premedications and other anesthetics, and in patient populations with diverse characteristics including underlying disease.

Adults: Approximately 2770 adult patients were exposed to ULTIVA in controlled clinical trials. The frequencies of adverse events during general anesthesia 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 $\geq 1\%$ of Adult Patients in General Anesthesia Studies* at the Recommended Doses† of ULTIVA

Adverse Event	Induction/Maintenance		Postoperative Analgesia				After Discontinuation	
	ULTIVA (n = 921)	Alfentanil/Fentanyl (n = 466)	ULTIVA (n = 261)	Morphine (n = 98)	ULTIVA (n = 929)	Alfentanil/Fentanyl (n = 466)		
Nausea	8 (<1%)	0	61 (22%)	15 (15%)	339 (36%)	202 (43%)		
Hypotension	178 (19%)	30 (6%)	0	0	16 (2%)	9 (2%)		
Vomiting	4 (<1%)	1 (<1%)	22 (8%)	5 (5%)	150 (16%)	91 (20%)		
Muscle rigidity	98 (11%)†	37 (8%)	7 (2%)	0	2 (<1%)	1 (<1%)		
Bradycardia	62 (7%)	24 (5%)	3 (1%)	3 (3%)	11 (1%)	6 (1%)		
Shivering	3 (<1%)	0	15 (5%)	9 (9%)	49 (5%)	10 (2%)		
Fever	1 (<1%)	0	2 (<1%)	0	44 (5%)	9 (2%)		
Dizziness	0	0	1 (<1%)	0	27 (3%)	9 (2%)		
Visual disturbance	0	0	0	0	24 (3%)	14 (3%)		
Headache	0	0	1 (<1%)	1 (1%)	21 (2%)	8 (2%)		
Respiratory depression	1 (<1%)	0	19 (7%)	4 (4%)	17 (2%)	20 (4%)		
Apnea	0	1 (<1%)	9 (3%)	2 (2%)	2 (<1%)	1 (<1%)		
Pruritus	2 (<1%)	0	7 (2%)	1 (1%)	22 (2%)	7 (2%)		
Tachycardia	6 (<1%)	7 (2%)	0	0	10 (1%)	8 (2%)		
Postoperative pain	0	0	7 (2%)					

Hematologic and Lymphatic: anemia, lymphopenia, leukocytosis, thrombocytopenia. The frequencies of adverse events from the clinical studies at the recommended doses of ULTIVA in cardiac surgery are given in Tables 6, 7, and 8. These tables represent adverse events collected during discrete phases of cardiac surgery. Any event should be viewed as temporally associated with drug administration and the phase indicated should not be perceived as the only time the event might occur.

Table 6: Adverse Events Reported in ≥1% of Patients in the Induction/Intubation and Maintenance Phases of Cardiac Surgery Studies at the Recommended Doses* of ULTIVA

Adverse Event	Induction/Intubation			Maintenance		
	ULTIVA (n = 227)	Fentanyl (n = 176)	Sufentanil (n = 41)	ULTIVA (n = 227)	Fentanyl (n = 176)	Sufentanil (n = 41)
Hypotension	18 (8%)	6 (3%)	7 (17%)	26 (11%)	6 (3%)	1 (2%)
Bradycardia	9 (4%)	5 (3%)	0	3 (1%)	1 (<1%)	1 (2%)
Hypertension	3 (1%)	2 (1%)	2 (5%)	6 (4%)	6 (3%)	1 (2%)
Constipation	9 (4%)	1 (<1%)	3 (7%)	0	0	1 (2%)
Muscle rigidity	2 (<1%)	2 (1%)	0	5 (2%)	8 (5%)	0
Premature ventricular beats	1 (<1%)	0	0	3 (1%)	1 (<1%)	0
Myocardial ischemia	0	0	0	7 (3%)	8 (5%)	1 (2%)
Atrial fibrillation	0	0	0	7 (3%)	3 (2%)	1 (2%)
Decreased cardiac output	0	0	0	5 (2%)	1 (<1%)	1 (2%)
Tachycardia	0	1 (<1%)	0	4 (2%)	2 (1%)	0
Coagulation disorder	0	0	0	4 (2%)	0	1 (2%)
Arrhythmia	0	0	0	3 (1%)	0	0
Ventricular fibrillation	0	0	0	3 (1%)	1 (<1%)	1 (2%)
Postoperative complication	0	0	0	3 (1%)	0	0
Third degree heart block	0	0	0	2 (<1%)	0	1 (2%)
Hemorrhage	0	0	0	2 (<1%)	0	1 (2%)
Perioperative complication	0	0	0	2 (<1%)	1 (<1%)	1 (2%)
Involuntary movements)	0	0	0	2 (<1%)	3 (2%)	0
Thrombocytopenia	0	0	1 (2%)	0	0	0
Oliguria	0	0	0	0	3 (2%)	0
Anemia	0	0	0	2 (<1%)	2 (1%)	0

*See Table 13 for recommended doses.

Table 7: Adverse Events Reported in ≥1% of Patients in the ICU Phase of Cardiac Surgery Studies at the Recommended Doses* of ULTIVA

Adverse Event	ULTIVA n = 227	Fentanyl n = 176	Sufentanil n = 41
Hypertension	14 (6%)	8 (5%)	2 (5%)
Hypotension	12 (5%)	3 (2%)	0
Tachycardia	9 (4%)	5 (3%)	0
Shivering	8 (4%)	3 (2%)	1 (2%)
Nausea	8 (4%)	3 (2%)	0
Hemorrhage	4 (2%)	1 (<1%)	1 (2%)
Postoperative complication	4 (2%)	5 (3%)	2 (5%)
Agitation	4 (2%)	1 (<1%)	1 (2%)
Ache	4 (2%)	0	0
Decreased cardiac output	3 (1%)	0	0
Arrhythmia	3 (1%)	0	0
Muscle rigidity	2 (<1%)	1 (<1%)	2 (5%)
Bradycardia	2 (<1%)	2 (1%)	0
Vomiting	1 (<1%)	2 (1%)	0
Premature ventricular beats	1 (<1%)	2 (1%)	0
Anemia	0	3 (2%)	0
Somnolence	0	0	1 (2%)
Fever	0	2 (1%)	0

*See Table 13 for recommended doses.

Table 8: Adverse Events Reported in ≥1% of Patients in the Post-Study Drug Phase of Cardiac Surgery Studies at the Recommended Doses* of ULTIVA

Adverse Event	ULTIVA n = 227	Fentanyl n = 176	Sufentanil n = 41
Nausea	90 (40%)	63 (36%)	16 (39%)
Vomiting	33 (15%)	28 (16%)	3 (7%)
Fever	30 (13%)	15 (9%)	0
Atrial fibrillation	27 (12%)	33 (19%)	4 (10%)
Constipation	20 (9%)	35 (20%)	3 (7%)
Pleural effusion	11 (5%)	2 (1%)	2 (5%)
Hypotension	8 (4%)	8 (5%)	0
Tachycardia	9 (4%)	15 (9%)	0
Postoperative complication	10 (4%)	6 (3%)	2 (5%)
Oliguria	7 (3%)	7 (4%)	1 (2%)
Confusion	7 (3%)	10 (6%)	5 (12%)
Ache	6 (3%)	2 (1%)	0
Anxiety	6 (3%)	6 (3%)	0
Headache	6 (3%)	2 (1%)	0
Perioperative complication	5 (2%)	7 (4%)	1 (2%)
Anemia	5 (2%)	5 (3%)	1 (2%)
Agitation	5 (2%)	3 (2%)	1 (2%)
Diarrhea	5 (2%)	1 (<1%)	1 (2%)
Edema	4 (2%)	6 (3%)	0
Dizziness	4 (2%)	3 (2%)	1 (2%)
Postoperative infection	5 (2%)	7 (4%)	0
Hypoxia	4 (2%)	5 (3%)	0
Apnea	4 (2%)	1 (<1%)	1 (2%)
Hypertension	3 (1%)	3 (2%)	0
Shivering	3 (1%)	1 (<1%)	0
Heartburn	3 (1%)	3 (2%)	0
Atrial flutter	3 (1%)	1 (<1%)	0
Arrhythmia	3 (1%)	5 (3%)	0
Hallucinations	0	3 (2%)	0
Pneumonia	3 (1%)	3 (2%)	1 (2%)
Pharyngitis	3 (1%)	1 (<1%)	1 (2%)
Decreased mental acuity	3 (1%)	1 (<1%)	0
Dyspnea	3 (1%)	1 (<1%)	0
Cough	3 (1%)	0	0
Decreased cardiac output	1 (<1%)	0	3 (7%)
Renal insufficiency	1 (<1%)	5 (3%)	0
Bradycardia	1 (<1%)	1 (<1%)	1 (2%)
Urine retention	2 (<1%)	3 (2%)	0
Cerebral infarction	2 (<1%)	2 (1%)	1 (2%)
Premature ventricular beats	2 (<1%)	3 (2%)	0
Cerebral ischemia	1 (<1%)	1 (<1%)	1 (2%)
Paresthesia	2 (<1%)	2 (1%)	0
Seizure	2 (<1%)	1 (<1%)	1 (2%)
Sleep disorder	1 (<1%)	1 (<1%)	1 (2%)
Bronchospasm	1 (<1%)	6 (3%)	0
Atelectasis	2 (<1%)	3 (2%)	0
Respiratory depression	2 (<1%)	3 (2%)	0
Chest edema	1 (<1%)	2 (1%)	0
Respiratory distress	2 (<1%)	0	1 (2%)
Hyperkalemia	2 (<1%)	3 (2%)	0
Electrolyte disorder	0	3 (2%)	0
Chest congestion	0	3 (2%)	0
Hemoptysis	0	2 (1%)	0
Facial pritis	0	2 (1%)	0
Hemorrhage	0	2 (1%)	0

(Continued on next page)

Table 9: Adverse Events Reported in ≥1% of Patients in the Post-Study Drug Phase of Cardiac Surgery Studies at the Recommended Doses* of ULTIVA (Continued)

Adverse Event	ULTIVA n = 227	Fentanyl n = 176	Sufentanil n = 41
Hematuria	0	1 (<1%)	1 (2%)
Visual disturbance(s)	0	1 (<1%)	1 (2%)
Hypokalemia	0	2 (1%)	0
Exacerbation of renal failure	0	0	1 (2%)
Blood in stool	0	0	1 (2%)
First degree heart block	0	0	1 (2%)
Pericarditis	0	0	1 (2%)

*See Table 13 for recommended doses.

Pediatrics: ULTIVA has been studied in 342 pediatric patients in controlled clinical trials for maintenance of general anesthesia. In the pediatric population (birth to 12 years), the most commonly reported events were nausea, vomiting, and shivering.

The frequencies of adverse events during general anesthesia with the recommended doses of ULTIVA are given in Table 9. Each patient was counted once for each type of adverse event. There were no adverse events ≥1% for any treatment group during the maintenance period in the pediatric patient general anesthesia studies.

Table 9: Adverse Events Reported in ≥1% of Pediatric Patients Receiving ULTIVA in General Anesthesia Studies at the Recommended Doses* of ULTIVA

Adverse Event	Recovery			Follow-up**		
	ULTIVA (n = 342)	Fentanyl (n = 103)	Bupivacaine (n = 86)	ULTIVA (n = 342)	Fentanyl (n = 103)	Bupivacaine (n = 86)
Cardiovascular: Asystole	0	0	0	0	0	0
Vomiting	40 (12%)	9 (9%)	10 (12%)	56 (16%)	8 (8%)	12 (14%)
Nausea	23 (8%)	7 (7%)	1 (1%)	17 (6%)	6 (6%)	5 (6%)
Shivering	9 (3%)	0	0	0	0	0
Rhonchi	8 (3%)	2 (2%)	0	0	0	0
Postoperative complication	5 (2%)	2 (2%)	0	4 (1%)	0	0
Stridor	4 (1%)	2 (2%)	0	1 (0)	0	0
Cough	4 (1%)	1 (<1%)	0	0	0	0

*See Table 11 for recommended doses.

**41 subjects receiving halothane (n=22), 10 (45%) experienced vomiting.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of remifentanyl in conjunction with one or more anesthetic agents in clinical practice. Because these events 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 remifentanyl.

Cardiovascular: Asystole.

Non-Site Specific: Anaphylactoid/anaphylactoid responses, which in some cases have been severe (e.g., shock).

DRUG ABUSE AND DEPENDENCE

ULTIVA is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and has the potential for being abused.

OVERDOSAGE

As with all potent opioid analgesics, overdosage would be manifested by an extension of the pharmacological actions of ULTIVA. Expected signs and symptoms of overdosage include: apnea, chest-wall rigidity, seizures, hypoxemia, hypotension, and bradycardia.

In case of overdosage or suspected overdosage, 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 or a μ -opioid antagonist may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed. Glycopyrrolate or atropine may be useful for the treatment of bradycardia and/or hypotension.

Intravenous administration of an opioid antagonist such as naloxone may be employed as a specific antidote to manage severe respiratory depression or muscle rigidity. Respiratory depression from overdosage with ULTIVA is not expected to last longer than the opioid antagonist, naloxone. Reversal of the opioid effects may lead to acute pain and sympathetic hyperactivity.

DOSE AND ADMINISTRATION

ULTIVA is for IV use only. Continuous infusions of ULTIVA should be administered only by an infusion device. The injective site should be close to the venous cannula and all IV tubing should be cleared at the time of discontinuation of infusion.

During General Anesthesia: ULTIVA is not recommended as the sole agent in general anesthesia because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and tachycardia. ULTIVA is synergistic with other anesthetics; therefore, clinicians may need to reduce doses of bispectral, propofol, isoflurane, and midazolam by up to 25% with the coadministration of ULTIVA. The administration of ULTIVA must be individualized based on the patient's response.

Table 10 summarizes the recommended doses in adult patients, predominantly ASA physical status I, II, or III.

Table 10: Dosing Guidelines in Adults — General Anesthesia and Continuing as an Analgesic into the Postoperative Care Unit or Intensive Care Settings*

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Infusion Dose Range of ULTIVA (mcg/kg/min)	Supplemental IV Bolus Dose of ULTIVA (mcg/kg)
Induction of Anesthesia (through intubation)	0.5 - 1*		
Maintenance of anesthesia with:			
Nitrous oxide (66%)	0.4	0.1 - 2	1
Isoflurane (0.4 to 1.5 MAC)	0.25	0.05 - 2	1
Propofol (100 to 200 mcg/kg/min)	0.25	0.05 - 2	1
Continuation as an analgesic into the immediate postoperative period	0.1	0.025 - 0.2	not recommended

*An initial dose of 1 mcg/kg may be administered over 30 to 60 seconds.

Table 11 summarizes the recommended doses in pediatric patients, predominantly ASA physical status I, II, or III. In pediatric patients, remifentanyl was administered with nitrous oxide or nitrous oxide in combination with halothane, sevoflurane, or isoflurane.

Table 11: Dosing Guidelines in Pediatric Patients — Maintenance of Anesthesia

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Infusion Dose Range of ULTIVA (mcg/kg/min)	Supplemental IV Bolus Dose of ULTIVA(mcg/kg)
*Maintenance of anesthesia in patients aged 1 to 12 years old with:			
Halothane (0.3 to 1.5 MAC)	0.25	0.05 - 1.3	1
Sevoflurane (0.3 to 1.5 MAC)	0.25	0.05 - 1.3	1
Isoflurane (0.4 to 1.5 MAC)	0.25	0.05 - 1.3	1
Maintenance of anesthesia for patients from birth to 2 months of age with:			
Nitrous oxide (70%)**	0.4	0.4 - 1.0	1***

*An initial dose of 1 mcg/kg may be administered over 30 to 60 seconds.

**The initial maintenance infusion regimen of Ultiva evaluated in full term pediatric patients from birth to 2 months of age undergoing pyloromyotomy was 0.4 mcg/kg/min, the approved adult regimen for use with N₂O. The clearance rate observed in neonates was highly variable and on average was two times higher than in the young healthy adult population. Therefore, while a starting infusion of 0.4 mcg/kg/min may be appropriate for some neonates, an increased infusion rate may be necessary to maintain adequate surgical anesthesia, and additional bolus doses may be required. The individual dose for each patient should be carefully titrated. The use of atropine may blunt the potential for bradycardia that can occur upon administration of Ultiva. (see CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients, and DOSAGE AND ADMINISTRATION, During Maintenance of Anesthesia).

*** Boluses of 1 mcg/kg were studied in ASA I and 2, full-term patients weighing at least 2500 gm, undergoing pyloromyotomy who received pretreatment with atropine. Some neonates, particularly those receiving supplementation with potent inhalation agents or neuraxial anesthesia, those with significant co-morbidities or undergoing significant fluid shifts, or those who have not been pretreated with atropine, may require smaller bolus doses to avoid hypotension and/or bradycardia.

During Induction of Anesthesia: ULTIVA should be administered at an infusion rate of 0.5 to 1 mcg/kg/min with a hypnotic or volatile agent for the induction of anesthesia. If endotracheal intubation is to occur less than 8 minutes after the start of the infusion of ULTIVA, then an initial dose of 1 mcg/kg may be administered over 30 to 60 seconds.

During Maintenance of Anesthesia: After endotracheal intubation, the infusion rate of ULTIVA should be decreased in accordance with the dosing guidelines in Tables 10 (adults) and 11 (pediatric patients). Due to the fast onset and short duration of action of ULTIVA, the rate of administration during anesthesia can be titrated upward in 25% to 100% increments in adult patients or up to 50% increments in pediatric patients, or downward in 25% to 50% decrements every 2 to 5 minutes to attain the desired level of μ -opioid effect. In response to light anesthesia or transient episodes of intense surgical stress, supplemental bolus doses of 1 mcg/kg may be administered every 2 to 5 minutes. At infusion rates >1 mcg/kg/min, increases in the concomitant anesthetic agents should be considered to increase the depth of anesthesia. See CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients, and DOSAGE AND ADMINISTRATION, Table 11 for additional information.

Continuation as an Analgesic into the Immediate Postoperative Period Under the Direct Supervision of an Anesthesia Practitioner: Infusions of ULTIVA may be continued into the immediate postoperative period for select patients for whom later transition to longer acting analgesics may be desired. The use of bolus injections of ULTIVA to treat pain during the postoperative period is not recommended. When used as an IV analgesic in the immediate postoperative period, ULTIVA should be initially administered by continuous infusion at a rate of 0.1 mcg/kg/min. The infusion rate may be adjusted every 5 minutes in 0.025-mcg/kg/min increments to balance the patient's level of analgesia and respiratory rate. Infusion rates greater than 0.2 mcg/kg/min are associated with respiratory depression (respiratory rate less than 8 breaths/min).

Guidelines for Discontinuation: Upon discontinuation of ULTIVA, the IV tubing should be cleared to prevent the inadvertent administration of ULTIVA at a later time.

Due to the rapid offset of action of ULTIVA, no residual analgesic activity will be present within 5 to 10 minutes after discontinuation. For patients undergoing surgical procedures where postoperative pain is generally anticipated, alternative analgesics should be administered prior to discontinuation of ULTIVA. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of follow-up care (see CLINICAL TRIALS).

Analgesic Component of Monitored Anesthesia Care: It is strongly recommended that supplemental oxygen be supplied to the patient whenever ULTIVA is administered.

Table 12 summarizes the recommended doses for monitored anesthesia care in adult patients, predominantly ASA physical status I, II, or III. ULTIVA has not been studied for use in children in monitored anesthesia care.

Table 12: Dosing Guidelines in Adults — Monitored Anesthesia Care

Method	Timing	ULTIVA Alone	ULTIVA + 2 mg Midazolam
Single IV Dose	Given 90 seconds before local anesthetic	1 mcg/kg over 30 to 60 seconds	0.5 mcg/kg over 30 to 60 seconds
Continuous IV Infusion	Beginning 5 minutes before local anesthetic	0.1 mcg/kg/min	0.05 mcg/kg/min

Single Dose: A single IV dose of 0.5 to 1 mcg/kg over 30 to 60 seconds of ULTIVA may be given 90 seconds before the placement of the local or regional anesthetic block (see PRECAUTIONS).

Continuous Infusion: When used alone as an IV analgesic component of monitored anesthesia care, ULTIVA should be initially administered by continuous infusion at a rate of 0.1 mcg/kg/min beginning 5 minutes before placement of the local or regional anesthetic block. **Because of the risk for respiratory depression, the infusion rate of ULTIVA should be decreased to 0.05 mcg/kg/min following placement of the block.** Thereafter, rate adjustments of 0.025 mcg/kg/min at 5-minute intervals may be used to balance the patient's level of analgesia and respiratory rate. Rates greater than 0.2 mcg/kg/min are generally associated with respiratory depression (respiratory rates less than 8 breaths/min). **Bolus doses of ULTIVA administered simultaneously with a continuous infusion of ULTIVA to spontaneously breathing patients are not recommended.**

Individualization of Dosage:

Use in Geriatric Patients: The starting doses of ULTIVA should be decreased by 50% in elderly patients (>65 years). ULTIVA should then be cautiously titrated to effect.

Use in Pediatric Patients: See Table 11 for dosing recommendations for use of ULTIVA in pediatric patients from birth to 12 years of age for maintenance of anesthesia. See CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients, and DOSAGE AND ADMINISTRATION, Table 11 and During Maintenance of Anesthesia for additional information.

ULTIVA has not been studied in pediatric patients for use in the immediate postoperative period or for use as a component of monitored anesthesia care.

Use in Coronary Artery Bypass Surgery: Table 13 summarizes the recommended doses for induction, maintenance, and continuation as an analgesic into the ICU in adult patients, predominantly ASA physical status III or IV. **To avoid hypotension during the induction phase, it is important to consider the concomitant medication regimens described in the CLINICAL TRIALS: Coronary Artery Bypass Surgery subsection.**

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Infusion Dose Range of ULTIVA (mcg/kg/min)	Supplemental IV Bolus Dose of ULTIVA (mcg/kg)
	Induction of Anesthesia (through intubation)	1	0.125 - 4
Maintenance of Anesthesia	1	0.125 - 4	0.5 - 1
Continuation as an analgesic into ICU		0.05 - 1	

* See CLINICAL TRIALS: Coronary Artery Bypass Surgery subsection for concomitant medication regimens. **Use in Obese Patients:** The starting doses of ULTIVA should be based on ideal body weight (IBW) in obese patients (greater than 30% over their IBW).

Preanesthetic Medication: The need for premedication and the choice of anesthetic agents