RFEN2-00

Ultiva®

for Injection

(remifentanil hydrochloride)

For IV Use Only

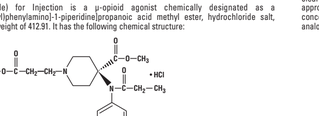
II only

Ultiva® for Injection (remifentanil hydrochloride) For IV Use Only II only

RFEN2-00 (03/09) -Rev. March, 2009

DESCRIPTION

ULTIVA (remifentanil hydrochloride) for Injection is a μ-opioid agonist chemically designated as a 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt, $C_{20}H_{28}N_2O_5{\cdot}HCl$, with a molecular weight of 412.91. 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 and dilution. Each vial contains 1, 2, or 5 mg of remifentanil base; 15 mg glycine; and hydrochloric acid to buffer the solutions to a nominal pH of 3 after reconstitution. When reconstituted as directed, ULTIVA and ULTIVA are clear and colorless and contain remifentanil hydrochloride (HCl) equivalent to 1 mg/mL of remifentanil base. The pH of reconstituted solutions of ULTIVA ranges from 2.5 to 3.5. Remifentanil HCl has a pKa of 7.07. Remifentanil 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.

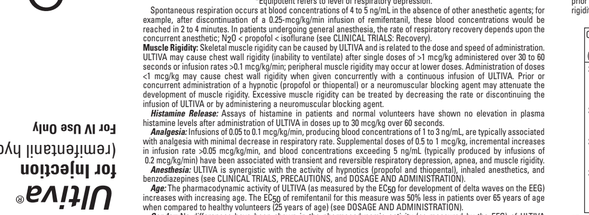
ULTIVA is rapidly metabolized by hydrolysis of the propanoic acid-methyl ester linkage by nonspecific blood and tissue esterases. ULTIVA is not a substrate for plasma cholinesterase (pseudocholinesterase) and, therefore, patients with atypical cholinesterase are expected to have a normal duration of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

Pharmacodynamics: The analgesic effects of ULTIVA are rapid in onset and offset. The adverse effects and side effects are dose dependent and similar to other μ-opioids. ULTIVA 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 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 drug 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 infusion administration 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 >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 bloset concentrations achieved. Peak hemodynamic effects occur approximately 1 minute after injection of ULTIVA or an infusion rate increase. Glycopyrrolate, atropine, and vagolytic neuromuscular blocking agents attenuate the hemodynamic effects associated with ULTIVA. When appropriate, bradycardia and hypotension can be reversed by decreasing or discontinuing the infusion of ULTIVA, or the dose of concomitant medications, 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. When ULTIVA 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 ULTIVA (see Figure 1).

Figure 1: Mean Equipotent* Doses of ULTIVA and Alfentanil Using CO_2-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 remifentanil, 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. Initiation of 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 hypnotic (propofol or thiopental) or 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.

Analgesia: Infusions of 0.05 to 0.1 mcg/kg/min, producing blood concentrations of 1 to 3 ng/mL, are typically associated with analgesia with minimal decrease in respiratory drive. Supplemental doses of 0.5 to 1 mcg/kg, incrementally 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, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Age: The pharmacodynamic activity of ULTIVA (as measured by the ED_{50} for development of delta waves on the EEG) increases with increasing age. The ED_{50} of remifentanil 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 Interactions: In animals the duration of muscle paralysis from succinylcholine is not prolonged by remifentanil.

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 ($PaCO_2$ <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 opioids. In patients receiving ULTIVA and nitrous oxide anesthesia, cerebrovascular reactivity to carbon dioxide remained intact. In humans, no epileptiform activity was seen on the EEG (n = 44) at remifentanil 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 Dysfunction: The pharmacodynamics of ULTIVA (ventilatory response to hypercarbia) are unaltered in patients with severe hepatic dysfunction awaiting liver transplant.

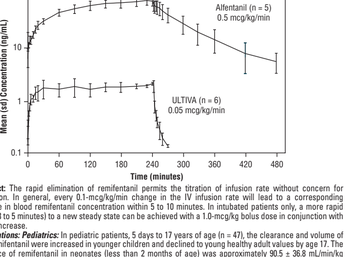
Pharmacokinetics: After IV doses administered over 60 seconds, the pharmacokinetics of remifentanil fit a three-compartment model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes. Since the terminal elimination component contributes less than 10% of the overall area under the concentration versus time curve (AUC), the effective biological 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 9 hours. Concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. The pharmacokinetics of remifentanil are unaffected by the presence of renal or hepatic impairment.

Distribution: The initial volume of distribution (V_d) of remifentanil is approximately 100 mL/kg and represents distribution throughout the blood and rapidly perfused tissues. Remifentanil 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]). Remifentanil is approximately 70% bound to plasma proteins of which two-thirds is binding to alpha-1-acid-glycoprotein.

Metabolism: Remifentanil 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-oxopropy)phenylamino]-1-piperidine]propanoic acid), and represents the principal metabolic pathway for remifentanil (>95%). The carboxylic acid metabolite is essentially inactive (1/4600 as potent as remifentanil in dogs) and is excreted by the kidneys with an elimination half-life of approximately 90 minutes. Remifentanil is not metabolized by plasma cholinesterase (pseudocholinesterase) and is not appreciably metabolized by the liver or lung.

Elimination: The clearance of remifentanil 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 remifentanil combined with a relatively small volume of distribution produces a short elimination half-life of approximately 5 to 10 minutes (see Figure 2). This value is consistent with the times taken for blood or effect site concentrations to fall by 50% (context-sensitive half-times) 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 remifentanil permits the titration of infusion rate without concern for prolonged duration. In general, every 0.1-mcg/kg/min change in the IV infusion rate will lead to a corresponding 2.5-ng/mL change in blood remifentanil concentration within 5 to 10 minutes. The mean infusion rate required during maintenance of anesthesia in healthy adults ranges from 0.3 mcg/kg/min (range 0.2 to 1.3 mcg/kg/min). The continuous infusion rate was decreased to 0.05 mcg/kg/min approximately 10 minutes prior to the end of surgery. Time to spontaneous purposeful movement was a median of 8 minutes (range 1 to 19 minutes). Time to extubation was a median of 9 minutes (range 2 to 19 minutes).

Study 3, an open-label, randomized, controlled trial (n = 271), compared ULTIVA (n = 185) with a regional anesthetic technique (n = 86) in children 1 to 12 years of age undergoing major abdominal, urological, or orthopedic surgery. Patients received a 0.25 mcg/kg/min infusion of ULTIVA following a 1.0 mcg/kg bolus or bupivacaine by epidural infusion, during with isoflurane and nitrous oxide after the induction of anesthesia. The mean infusion rate required during maintenance of anesthesia was 0.25 mcg/kg/min (range 0 to 0.75 mcg/kg/min). Both treatments were effective in attenuating responses to skin incision during surgery. The hemodynamic profile of the ULTIVA group was consistent with a less stress based general anesthetic technique. Time to spontaneous purposeful movement was a median of 15 minutes (range, 2 to 75 minutes) in the remifentanil group. Time to extubation was a median of 13 minutes (range, 4 to 31 minutes) in the remifentanil group.

Study 4, an open-label, randomized, controlled trial (n=60), compared ULTIVA (n = 38) with halothane (n = 22) in ASA 1 or 2, full term neonates and infants ≤8 weeks of age weighing at least 2500 grams who were undergoing pyloromyotomy. After induction of anesthesia, which included the administration of atropine, patients received 0.4 mcg/kg/min of ULTIVA or 0.4% halothane with 70% nitrous oxide for initial maintenance of anesthesia and then both agents were adjusted according to clinical response. Bolus doses of 1 mcg/kg administered over 30 to 60 seconds were used to treat brief episodes of hypertension and tachycardia, and infusion rates were increased by 50% to treat sustained hypertension and tachycardia. The range of infusion rates of ULTIVA during maintenance of anesthesia was 0.4 to 1 mcg/kg/min. [Seventy-one percent (71%) of Ultiva patients required supplementary boluses or rate increases from the starting dose of 0.4 mcg/kg/min to treat hypertension, tachycardia, movement or somatic signs of light anesthesia. Twenty-four percent of the patients required an increase from the initial rate of 0.4 mcg/kg/min prior to incision and 26% of patients required an infusion rate between 0.8 and 1.0 mcg/kg/min, most often during gastric manipulation. The continuous infusion rate was decreased to 0.05 mcg/kg/min approximately 10 minutes before the end of surgery. In the ULTIVA group, median time from discontinuation of anesthesia to spontaneous purposeful movement was 6.5 minutes (range, 1 to 13 minutes) and median time to extubation was 8.5 minutes (range, 1 to 14 minutes). The initial maintenance infusion regimen of Ultiva evaluated in pediatric patients from birth to 2 months of age was 0.4 mcg/kg/min, the approved adult regimen for use with N_2O. The clearance rate observed in the neonatal population 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. (See CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients, and DOSAGE AND ADMINISTRATION, Table 11.

No pediatric patients in the ulcerative colitis study receiving ULTIVA required naloxone during the immediate postoperative recovery period.

Coronary Artery Bypass Surgery: ULTIVA was originally administered to 225 subjects undergoing elective CABG surgery in two dose-ranging studies without active comparators. Subsequently, two double-blind, double-dummy clinical studies (N = 426) evaluated ULTIVA (n = 226) at recommended doses versus active comparators (n = 198).

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-mg/kg morphine IV as premedication. Anesthesia was induced using ULTIVA 10-mg/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 mg/kg or vecuronium 0.15 mg/kg. Patients were 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 10 mcg/kg was administered over 3 minutes. All subjects received sufficient titrated initially to end tidal concentration of 0.5%. During maintenance, the group randomized to ULTIVA received as needed 0.5-1 mcg/kg/min ULTIVA boluses (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 undergoing elective CABG surgery with poor left ventricular function (ejection fraction <0.35). Subjects received oral lorazepam 40 mg/kg as premedication. Anesthesia was induced using etomidate and loss of consciousness, followed by a low-dose propofol infusion (3 mg/kg/hr) and pancuronium 0.15 mg/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 bolus doses of ULTIVA (0.5 mcg/kg) and infusion rate increases of 0.5 to 1 mcg/kg/min (maximum rate allowed was 4 mcg/kg/min) of ULTIVA were administered to one group; while the fentanyl 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 remifentanil regimen effectively attenuated response to maximal sternal spread generally better than the dose and regimen studied for the active control (fentanyl). While this provides evidence for the efficacy of remifentanil as an analgesic in this setting, caution must be exercised in interpreting these results as evidence of superiority of remifentanil 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. In these studies, ventilation was controlled to maintain a predicted $PaCO_2$ 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) and 10 minutes (range -1 to 19 minutes), respectively. 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 higher incidence of bradycardia (6%) receiving ULTIVA and fentanyl had hypotension during induction. Anesthesia was maintained with nitrous oxide and ULTIVA at a mean infusion rate of 0.23 mcg/kg/min (range 0.1 to 0.4) compared with a fentanyl mean infusion rate of 0.04 mcg/kg/min (range 0.02 to 0.07). Supplemental doses were administered as needed to 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). 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 60 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 cardiovascular 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 1 confirmatory study in two efficacy studies, the dose-finding studies, the dose-finding studies of ULTIVA and incremental infusion rate increases ≥0.05 mcg/kg/min led to respiratory depression and muscle rigidity. **Bolus doses of 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. Study 1, 50% decreases in respiratory rate were made if respiratory rate decreased below 8 breaths/min. With this difference in criteria for infusion rate decrease, the incidence of respiratory depression was lower in Study 1 (14%) 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 mg/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 who received morphine. Respiratory depression requiring intervention occurred more frequently in 45% of morphine patients. For patients who received ULTIVA, morphine sulfate (0.15 mg/kg) was administered in divided doses 5 and 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 demonstrated that use of sedation as an endpoint for titration of ULTIVA led to a high incidence of muscle rigidity (69%) and respiratory depression. With these studies as guides, three other studies titrated ULTIVA to specific clinical endpoints, and adequate respiration (respiratory rate >8 breaths/min) with a corresponding lower incidence of muscle rigidity (3%) and respiratory depression. With doses of midazolam >2 mg (4 to 8 mg), the dose of ULTIVA could be decreased by 50%, but the incidence of respiratory depression rose to 32%.

The efficacy of a single dose of ULTIVA (1.0 mcg/kg over 30 seconds) was compared to alfentanil (7 mcg/kg over 30 seconds) in patients undergoing ophthalmic surgery. More patients receiving ULTIVA were pain free at the time of the nerve block (77% versus 44%, $P = 0.02$) and more experienced nausea (12% versus 4%) than those receiving alfentanil.

In a randomized, controlled study (n = 118), ULTIVA 0.5 mcg/kg over 30 to 60 seconds followed by a continuous infusion of 0.1 mcg/kg/min, was compared to a propofol bolus (500 mcg/kg) followed by a continuous infusion (50 mcg/kg/min) in patients who received a local or regional anesthetic nerve block 5 minutes later. Patients who reported no or severe pain during placement of the block was similar between groups (2% with ULTIVA and 8% with propofol, $P = 0.2$) and more patients receiving ULTIVA experienced nausea (26% versus 2%, $P < 0.001$). The final mean infusion rate of ULTIVA was 0.08 mcg/kg/min.

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, ULTIVA was administered as a 0.5-mcg/kg dose over 30 seconds followed by a continuous infusion of 0.05 mcg/kg/min and midazolam 2 mg was administered 5 minutes later. The occurrence of moderate or severe pain during the local anesthetic injection was similar between groups (16% and 20%). Other effects for ULTIVA alone and ULTIVA/midazolam were: respiratory depression with oxygen desaturation (SPO2<90%), 5% and 2%; nausea, 8% and 2%; and pruritus, 23% and 12%. Titration of ULTIVA resulted in prompt resolution of respiratory depression (median 3 minutes, range 0 to 6 minutes). The final mean infusion rate of ULTIVA was 0.12 mcg/kg/min (range 0.03 to 0.3) for the group receiving ULTIVA alone and 0.07 mcg/kg/min (range 0.02 to 0.2) for the group receiving ULTIVA/midazolam.

Because of the risk for hypoventilation, the infusion rate of ULTIVA should be decreased to 0.05 mcg/kg/min following placement of the local or regional block and titrated thereafter in increments of 0.025 mcg/kg/min at 5-minute intervals. Bolus doses of ULTIVA administered simultaneously with a continuous infusion of ULTIVA to spontaneously breathing patients are not recommended.

INDICATIONS AND USE

ULTIVA is indicated for IV administration:

1. As an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures.
2. For continuation as an analgesic into the immediate postoperative period in adult patients under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting.
3. As an analgesic component of monitored anesthesia care in adult patients.

CONTRAINDICATIONS

Due to the presence of glycine in the formulation, ULTIVA is contraindicated for epidural or intrathecal administration. ULTIVA is also contraindicated in patients with known hypersensitivity to fentanyl analogs.

WARNINGS

Continuous infusions of ULTIVA should be administered only by an infusion device. **IV bolus administration of ULTIVA should be used only during the maintenance of general anesthesia.** In noninfubated patients, single doses of ULTIVA should be administered over 30 to 60 seconds.

Interruption of an infusion of ULTIVA will result in rapid offset of effect. Rapid clearance and lack of drug accumulation result in rapid dissipation of respiratory depressant and analgesic effects upon discontinuation of ULTIVA at recommended doses. Discontinuation of an infusion of ULTIVA should be preceded by the administration of adequate postoperative analgesia.

Injections of ULTIVA should be made into IV tubing at or close to the venous cannula. Upon discontinuation of ULTIVA, the IV tubing should be flushed to prevent the inadvertent administration of ULTIVA at a later point in time. **Failure to adequately clear the IV tubing to remove residual ULTIVA has been associated with the appearance of respiratory depression, apnea, and muscle rigidity upon the administration of additional fluids or medications through the same IV tubing.**

USE OF ULTIVA IS ASSOCIATED WITH APNEA AND RESPIRATORY DEPRESSION. ULTIVA SHOULD BE ADMINISTERED ONLY BY PERSONS NOT INVOLVED IN THE CONDUCT OF THE SURGICAL OR DIAGNOSTIC PROCEDURE. OXYGEN SATURATION SHOULD BE MONITORED ON A CONTINUOUS BASIS.

RESUSCITATIVE AND INTUBATION EQUIPMENT, OXYGEN, AND AN OPIOID ANTAGONIST MUST BE READILY AVAILABLE.

Respiratory depression in spontaneously breathing patients is generally managed by decreasing the rate of the infusion of ULTIVA by 50% or by temporarily discontinuing the infusion.

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 after infusion rates >0.1 mcg/kg/min. Single doses <1 mcg/kg may cause chest wall rigidity when given concurrently with a continuous infusion of ULTIVA.

Muscle rigidity caused by ULTIVA should be managed in the context of the patient's clinical condition. Muscle rigidity occurring during the induction of anesthesia should be treated by the administration of a neuromuscular blocking agent and the concurrent induction medications.

Muscle rigidity seen during use of ULTIVA in spontaneously breathing patients 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. In the case of life-threatening muscle rigidity, a rapid onset neuromuscular blocker or naloxone may be administered.

ULTIVA should not be administered into the same IV tubing with blood due to potential inactivation by nonspecific esterases in blood products.

PRECAUTIONS

Vital signs and oxygenation must be continually monitored during the administration of ULTIVA.

General: Bradycardia has been reported with ULTIVA and is responsive to ephedrine or anticholinergic drugs, such as atropine and glycopyrrolate.

Hypotension has been reported with ULTIVA and is responsive to decreases in the administration of ULTIVA or to IV fluids or catecholamine (ephedrine, epinephrine, norepinephrine, etc.) administration.

Intraoperative awareness has been reported in patients under 55 years of age when ULTIVA has been administered with propofol infusion rates of ≤75 mcg/kg/min.

Rapid Offset of Action: WITHIN 5 TO 10 MINUTES AFTER THE DISCONTINUATION OF ULTIVA, NO RESIDUAL ANALGESIC ACTIVITY WILL BE EXPECTED. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Standard monitoring should be maintained in the postoperative period to ensure adequate recovery without stimulation. For patients undergoing surgical procedures where postoperative pain is generally anticipated, other analgesics should be administered prior to the discontinuation of ULTIVA.

ULTIVA should not be used as a sole agent for induction of anesthesia because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and chest wall rigidity.

Pediatric Use: The efficacy and safety of ULTIVA as an analgesic agent for use in the maintenance of general anesthesia in outpatient and inpatient pediatric surgery have been established in controlled clinical trials in pediatric patients from birth to 12 years (see CLINICAL TRIALS).

The initial maintenance infusion regimen of Ultiva evaluated in pediatric patients from birth to 2 months of age was 0.4 mcg/kg/min, the approved adult regimen for use with N_2O. The clearance rate observed in neonates was highly variable and on average was two times higher than the young healthy adult population. Therefore, while a starting infusion rate 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. (See CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients, and DOSAGE AND ADMINISTRATION, Table 11 and During Maintenance of Anesthesia).

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

Geriatric Use: Of the total number of subjects in clinical studies of ULTIVA, 486 were 65 and over (age range 66 to 90 years). While the effective biological half-life of remifentanil is unchanged, elderly patients have been shown to be more sensitive to the pharmacodynamic effects of remifentanil. The recommended starting dose of ULTIVA should be decreased by 50% in patients over 65 years of age (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Use in Morbidly Obese Patients: As for all patient opioids, caution is required with use in morbidly obese patients because of alterations in cardiovascular and respiratory physiology (see DOSAGE AND ADMINISTRATION).

Long-term Use in the ICU: No data are available on the long-term (longer than 16 hours) use of ULTIVA as an analgesic in the ICU.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with remifentanil.

Remifentanil did not induce gene mutation in prokaryotic cells *in vitro* and was not genotoxic in the *in vivo* rat hepatocyte unscheduled DNA synthesis assay. No clastogenic effect was seen in cultured Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. In the *in vitro* mouse lymphoma assay, mutagenicity was seen only with metabolic activation.

Remifentanil has been shown to reduce fertility in male rats when tested after 70+ days of daily IV administration of 0.5 mg/kg, or approximately 40 times the maximum recommended human dose (MRHD) in terms of mg/m2 of body surface area. The fertility of female rats was not affected at IV doses as high as 1 mg/kg when administered for at least 15 days before mating.

Pregnancy Category C: Teratogenic effects were not observed following administration of remifentanil at doses up to 5 mg/kg in rats and 0.8 mg/kg in rabbits. These doses are approximately 400 times and 125 times the MRHD, respectively, in terms of mg/m2 of body surface area. Administration of radiolabeled remifentanil to pregnant rabbits and rats demonstrated significant placental transfer to fetal tissue. There are no adequate and well-controlled studies in pregnant women. ULTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of remifentanil to rats throughout late gestation and lactation at IV doses up to 5 mg/kg, or approximately 400 times the MRHD in terms of mg/m2 of body surface area, had no significant effect on the survival, development, or reproductive performance of the F1 generation.

Metabolic and Nutritional Disorders: Intrathecal administration of the glycine formulation without remifentanil to dogs caused agitation, pain, 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 has been the only adverse event associated with administration of ULTIVA.

Labor and Delivery: Respiratory depression and other opioid 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 peak concentrations of remifentanil in the fetus occurred within 5 minutes of the start of the trial, the average maternal remifentanil 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 remifentanil concentrations was approximately 30% suggesting metabolism of remifentanil in the placenta.

Nursing Mothers: It is not known whether remifentanil is excreted in human milk. After receiving radioactive-labeled remifentanil, 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 are dose-related and may be minimized or decreased by 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.

Table 3: Adverse Events Reported in ≥1% of Adult Patients in General Anesthesia Studies* at the Recommended Doses† of ULTIVA

	Induction/ Maintenance		Postoperative Analgesia		After Discontinuation	
Adverse Event	ULTIVA (n = 921)	Alfentanil/ Fentanyl (n = 466)	ULTIVA (n = 281)	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	16 (2%)	9 (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	7 (2%)	0	4 (<1%)	5 (1%)
Hypertension	10 (1%)	7 (2%)	5 (2%)	3 (3%)	12 (1%)	8 (2%)
Agitation	2 (<1%)	0	3 (1%)	1 (1%)	6 (<1%)	1 (<1%)
Hypoxia	0	0	1 (<1%)	0	10 (1%)	7 (2%)

*Does not include adverse events from cardiac studies or the neonatal study. See Tables 6, 7, and 8 for cardiac information.

†See Table 10 for recommended doses. **Not all doses of ULTIVA were equipotent to the comparator opioid. Administration of ULTIVA at doses >1 mcg/kg/min res

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

	Induction/Intubation			Maintenance		
Adverse Event	**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%)	8 (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 movement(s)	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%)	1 (2%)
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%)	26 (15%)	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%)	1 (2%)
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	3 (1%)	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
Pulmonary 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 ptosis	0	2 (1%)	0
Hemorrhage	0	2 (1%)	0

(Continued on next page)

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 (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

	Recovery			Follow-up**		
Adverse Event	ULTIVA (n = 342)	Fentanyl (n = 103)	Bupivacaine (n = 86)	ULTIVA (n = 342)	Fentanyl (n = 103)	Bupivacaine (n = 86)
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	0	0	0
Cough	4 (1%)	1 (<1%)	0	0	0	0

*See Table 11 for recommended doses.

**In 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 remifentanil in conjunction with one or more anesthetic 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.

Cardiovascular: Asystole.

Non-Site Specific: Anaphylactic/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.

DOSAGE AND ADMINISTRATION

ULTIVA is for IV use only. **Continuous infusions of ULTIVA should be administered only by an infusion device. The injection 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 thiopental, propofol, isoflurane, and midazolam by up to 75% 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, predominately 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 Setting*

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, remifentanil 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 N_2O. 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 1 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, predominately 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
	After local anesthetic	0.05 mcg/kg/min (Range: 0.025 - 0.2 mcg/kg/min)	0.025 mcg/kg/min (Range: 0.025 - 0.2 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 hypoventilation, 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.**

Table 13: Dosing Recommendations* — Coronary Artery Bypass Surgery

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		
Maintenance of Anesthesia	1	0.125 - 4	0.5 - 1
Continuation as an analgesic into ICU	1	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 must be individualized. In clinical studies, patients who received ULTIVA frequently received a benzodiazepine premedication.

Preparation for Administration: To reconstitute solution, add 1 mL of diluent 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 recommended final concentration of 20, 25, 50, or 250 mcg/mL prior to administration (see Table 14). ULTIVA should not be administered without dilution.**

Table 14: Reconstitution and Dilution of ULTIVA

Final Concentration	Amount of ULTIVA in Each Vial	Final Volume After Reconstitution and Dilution
20 mcg/mL	1 mg	50 mL
	2 mg	100 mL
	5 mg	250 mL
25 mcg/mL	1 mg	40 mL
	2 mg	80 mL
	5 mg	200 mL
50 mcg/mL	1 mg	20 mL
	2 mg	40 mL
	5 mg	100 mL
250 mcg/mL	5 mg	20 mL

Continuous IV infusions of ULTIVA should be administered only by an infusion device. Infusion rates of ULTIVA can be individualized for each patient using Table 15:

Table 15: IV Infusion Rates of ULTIVA (mL/kg/h)

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate (mL/kg/h)			
	20 mcg/mL	25 mcg/mL	50 mcg/mL	250 mcg/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

When ULTIVA is used as an analgesic component of monitored analgesia care, a final concentration of 25 mcg/mL is recommended. When ULTIVA is used for pediatric patients 1 year of age and older, a final concentration of 20 or 25 mcg/mL is recommended. Table 16 is a guideline for milliliter-per-hour delivery for a solution of 20 mcg/mL with an infusion device.

Table 16: IV Infusion Rates of ULTIVA (mL/h) for a 20-mcg/mL Solution

Infusion Rate (mcg/kg/min)	Patient Weight (kg)						
	5	10	20	30	40	50	60
0.0125	0.188	0.375	0.75	1.125	1.5	1.875	2.25
0.025	0.375	0.75	1.5	2.25	3.0	3.75	4.5
0.05	0.75	1.5	3.0	4.5	6.0	7.5	9.0
0.075	1.125	2.25	4.5	6.75	9.0	11.25	13.5
0.1	1.5	3.0	6.0	9.0	12.0	15.0	18.0
0.15	2.25	4.5	9.0	13.5	18.0	22.5	27.0
0.2	3.0	6.0	12.0	18.0	24.0	30.0	36.0
0.25	3.75	7.5	15.0	22.5	30.0	37.5	45.0
0.3	4.5	9.0	18.0	27.0	36.0	45.0	54.0
0.35	5.25	10.5	21.0	31.5	42.0	52.5	63.0
0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 17 is a guideline for milliliter-per-hour delivery for a solution of 25 mcg/mL with an infusion device.

Table 17: IV Infusion Rates of ULTIVA (mL/h) for a 25-mcg/mL Solution

Infusion Rate (mcg/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 18 is a guideline for milliliter-per-hour delivery for a solution of 50 mcg/mL with an infusion device.

Table 18: IV Infusion Rates of ULTIVA (mL/h) for a 50-mcg/mL Solution

Infusion Rate (mcg/kg/min)	Patient Weight (kg)							
	30	40	50	60	70	80	90	100
0.025					2.1	2.4	2.7	3.0
0.05		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 19 is a guideline for milliliter-per-hour delivery for a solution of 250 mcg/mL with an infusion device.

Table 19: IV Infusion Rates of ULTIVA (mL/h) for a 250-mcg/mL Solution

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

COMPATIBILITY AND STABILITY

Reconstitution and Dilution Prior to Administration: ULTIVA is stable for 24 hours at room temperature after reconstitution and further dilution to concentrations of 20 to 250 mcg/mL with the IV fluids listed below.

Sterile Water for Injection, USP
5% Dextrose Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
0.9% Sodium Chloride Injection, USP
0.45% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP

ULTIVA is stable for 4 hours at room temperature after reconstitution and further dilution to concentrations of 20 to 250 mcg/mL with Lactated Ringer's Injection, USP.

ULTIVA has been shown to be compatible with these IV fluids when coadministered into a running IV administration set.

Compatibility With Other Therapeutic Agents: ULTIVA has been shown to be compatible with DIPRIVAN® (propofol) Injection when coadministered into a running IV administration set. The compatibility of ULTIVA with other therapeutic agents has not been evaluated.

Incompatibilities: Nonspecific esterases in blood products may lead to the hydrolysis of remifentanil to its carboxylic acid metabolite. Therefore, administration of ULTIVA into the same IV tubing with blood is not recommended.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product should be a clear, colorless liquid after reconstitution and free of visible particulate matter.

ULTIVA does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

HOW SUPPLIED

ULTIVA should be stored at 2° to 25°C (36° to 77°F). ULTIVA for IV use is supplied as follows:

NDC Number	Container	Concentration	Quantity
67457-198-03	3 mL Vial	1 mg lyophilized powder	Box of 10
67457-198-05	5 mL Vial	2 mg lyophilized powder	Box of 10
67457-198-10	10 mL Vial	5 mg lyophilized powder	Box of 10

ULTIVA is a registered trademark of Glaxo Group Limited.
DIPRIVAN® is a registered trademark of Zeneca Pharmaceuticals.
US Patent Nos. 5,019,583; and 5,866,591

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