Dosing Guide

FOR INJECTION
ULTIVA®
(remifentanil HCl)

For more information, visit www.ultiva.com.

INDICATIONS

ULTIVA® (remifentanil HCl) for Injection is indicated for intravenous administration:

- As an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures
- 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
- As an analgesic component of monitored anesthesia care in adult patients

WARNING: ADDICTION, ABUSE, AND MISUSE
ULTIVA exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTIVA.

Please see Important Safety Information, including boxed warning on page 3.

RECONSTITUTION AND DILUTION PRIOR TO ADMINISTRATION

Final concentration (mcg/mL)	Amount of ULTIVA in each vial (mg)	Final volume after reconstitution and dilution (mL)
25	1 2 5	40 80 200
50	1 2 5	20 40 100

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.**

ULTIVA is a single dose vial and does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions

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.

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

ULTIVA should not be administered without dilution.

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.

Please see the enclosed full Prescribing Information, including boxed warning, for all precautions, warnings, contraindications, adverse events, and complete dosing guidelines.

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ADULT DOSING GUIDELINES
Adult General Anesthesia

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Range of Infusion Dose 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.

ADULT 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)

When used alone as an IV analgesic component of monitored anesthesia care, ULTIVA® (remifentanil HCl) for Injection 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.

ULTIVA has not been studied for use in children in monitored anesthesia care

- **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**
- **Bolus doses of ULTIVA administered simultaneously with a continuous infusion of ULTIVA to spontaneously breathing patients are not recommended**

Continuous infusions of ULTIVA should be administered only by an infusion device. Interruption of an infusion of ULTIVA will result in rapid offset of effect. Discontinuation of Ultiva should be preceded by the establishment of adequate postoperative analgesia.

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

INFUSION GUIDELINES IN mL/h FOR 50 mcg/mL SOLUTIONS

Infusion rate (mcg/kg/min)	Patient weight (kg)							
	30	40	50	60	70	80	90	100
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

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.

DRUG INTERACTIONS

Clinically Significant Drug Interactions with ULTIVA include: Benzodiazepines and other Central Nervous System (CNS) Depressants, Serotonergic Drugs, Monoamine Oxidase Inhibitors (MAOIs), Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics. *See table 18 in Prescribing Information.

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

PEDIATRIC DOSING GUIDELINES

Pediatric General Anesthesia

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Range of Infusion Dose ULTIVA (mcg/kg/min)	Supplemental IV Bolus Dose of ULTIVA (mcg/kg)
Maintenance of anesthesia in patients aged 1 to 12 years old with[a]:			
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%)[b]	0.4	0.4 – 1.0	1[c]

*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. (In the full Prescribing Information, 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 g, undergoing pyloromyotomy who received pretreatment with atropine. Some neonates, particularly those receiving supplementation with potent inhalation agents or neuraxial anesthesia, those with significant comorbidities 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.Please see the enclosed full PI, including boxed warning for complete dosing guidelines.

WARNING: ADDICTION, ABUSE, AND MISUSE
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Important Safety Information

ULTIVA is contraindicated for epidural or intrathecal administration due to the presence of glycine in the formulation and in patients with hypersensitivity to remifentanil (eg, anaphylaxis).

ULTIVA contains remifentanil, a Schedule II controlled substance. Because opioids are sought by drug abusers and people with addiction disorders, employ strategies to reduce the risks such as proper storage and control practices.

Serious, life-threatening, or fatal respiratory depression has been reported with opioids. ULTIVA should be administered only by persons specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids. Monitor patients closely, particularly during initiation and titration. Resuscitative and intubation equipment, oxygen, and opioid antagonists 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.

IMPORTANT SAFETY INFORMATION CONTINUED

Hypotension, profound sedation, respiratory depression, coma, and death may result from the concomitant use of ULTIVA with benzodiazepines or other CNS depressants. Patients should be advised to avoid alcohol for 24 hours after surgery.

A potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue ULTIVA if serotonin syndrome is suspected.

Continuous infusions of ULTIVA should be administered only by an infusion device. Interruption of an infusion of ULTIVA will result in rapid offset of effect. Discontinuation of ULTIVA should be preceded by the establishment of adequate postoperative analgesia.

IV tubing must be cleared to remove residual ULTIVA, which has been associated with respiratory depression, apnea, and muscle rigidity upon the administration of additional fluids or medications through the same IV tubing.

Skeletal muscle rigidity can be caused by ULTIVA and is related to the dose and speed of administration. ULTIVA may cause chest wall rigidity after single doses of >1 mcg/kg administered over 30 to 60 seconds, or after infusion rates >0.1 mcg/kg/min.

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

Bradycardia has been reported with ULTIVA and is responsive to ephedrine or anticholinergic drugs. Monitor heart rate during dosage initiation and titration.

Hypotension has been reported with ULTIVA and is responsive to decreases in administration, or to IV fluid or catecholamine (ephedrine, epinephrine, norepinephrine, etc.) administration. Monitor blood pressure during dosage initiation and titration.

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.

Monitor for sedation and respiratory depression in patients susceptible to the intracranial effects of carbon dioxide retention.

Standard monitoring of patients should be maintained in the postoperative period to ensure adequate recovery without stimulation.

Most common adverse reactions (incidence ≥1%) were respiratory depression, bradycardia, hypotension, and skeletal muscle rigidity.

Please see full Prescribing Information, including Boxed Warning.

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