INDICATIONS AND IMPORTANT RISK INFORMATION

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

IMPORTANT RISK INFORMATION
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.

Please see Important Risk Information continued on page 10, and accompanying full Prescribing Information in pocket for all precautions, warnings, contraindications, and adverse events.
Different than other IV opioid analgesics

Chemical structure allows for rapid metabolism

- Unlike other opioids, which are metabolized through the liver, Remi is rapidly metabolized by hydrolysis via nonspecific blood and tissue esterases.
- Remi is rapidly broken down to an essentially inactive metabolite, so offset of analgesic effect and recovery from intraoperative opioid analgesia can be rapid.

The key to Remi metabolism is this ester

Allows for metabolism by nonspecific blood and tissue esterases rather than the liver or lung.

Remi produces adverse events that are characteristic of μ-opioids, such as respiratory depression, apnea, tachycardia, bradycardia, hypotension, hypertension, and skeletal muscle (including chest wall) rigidity.

Remifentanil is commonly referred to as Remi by anesthesia providers.

Within 5 to 10 minutes after discontinuation of Remi, no residual analgesic activity will be present. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Other analgesics should be administered prior to discontinuation of Remi where postoperative pain is anticipated.

Continuous infusions of Remi should be administered only by an infusion device and continuous monitoring is necessary. Interruption of infusion will result in rapid offset of effect.

Normal recovery score at 30 minutes was achieved by 81% of Remi patients versus 61% of fentanyl patients. Recovery rates were similar at 45 minutes.

Remi should be used with caution in pediatric, geriatric, and morbidly obese patients due to high variability in pharmacodynamics and dose/response.

Pharmacokinetics and pharmacodynamics are not altered in patients with hepatic and renal impairment.

Well-established hemodynamic profile.

Rapid response to dose adjustment with peak effect reached in 1 to 2 minutes.

No accumulation in adipose tissue.

No increase in duration of action with prolonged administration.

Synergistic effect may require reduction in dosage of other anesthesia drugs.

Rapid recovery to have patients alert sooner than with fentanyl, even after long procedures.

Pharmacokinetics and pharmacodynamics

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After Remi-desflurane, the digital symbol substitution test (DSST) and Trieger dot test were impaired significantly less at 30 minutes (and also at 60 minutes for the DSST).

There was no significant difference in length of stay between the treatment groups. Median time between end of surgery and eligibility for extubation: 295 minutes (Remi) vs 375 minutes (sufentanil) ($P<0.05$).

The study recognized that both Remi and fentanyl allowed for early extubation.
The value of Remifentanil

**Cardiovascular surgery**

- Helps maintain intraoperative pain control and facilitate early extubation\(^1,9,10,11\)
- Helps manage the intraoperative stress response\(^9,12\)
- Better protects against intraoperative stimuli at skin incision and maximal sternal spread than sufentanil\(^5\)
- Maintains hemodynamic stability in cardiac procedures\(^11,9,11\)

Within 5 to 10 minutes after discontinuation of Remi, no residual analgesic activity will be present. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Other analgesics should be administered prior to discontinuation of Remi where postoperative pain is anticipated.

*There was no significant difference in length of stay between treatment groups. Median time between end of surgery and eligibility for extubation: 295 minutes (Remi) vs 375 minutes (sufentanil) (\(P<0.05\)).\(^9\)

\(^1\)The study recognized both Remi and fentanyl allowed for early extubation.\(^10\)

\(^2\)Tachycardia, bradycardia, hypotension, and hypertension have been reported with Remi.\(^1\)

\(^5\)The authors noted the results must be interpreted cautiously since cardiopulmonary bypass and aortic cross-clamp times were significantly shorter in the Remi group.\(^12\)

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> “…in patients undergoing CPB [cardiopulmonary bypass] for coronary revascularization and/or cardiac valve repair, patients anesthetized with remifentanil were eligible for postoperative extubation earlier than patients who had undergone these procedures under sufentanil anesthesia.”\(^9\)


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**Carotid artery surgery**

- Rapid response allows for rapid adjustment of depth of analgesia\(^*\)**\(^1\)
- Maintains hemodynamic stability in carotid artery surgery\(^2\)
- Allows early neurological evaluation with rapid return of psychomotor and cognitive function\(^2,13\)
- Rapid postoperative awakening and recovery following carotid artery surgery\(^2\)

*Significantly (\(P<0.05\)) more patients in the sufentanil group experienced a hemodynamic, somatic, or autonomic response at skin incision and maximal sternal spread vs patients in the Remi group. No differences between groups were found at intubation, sternotomy, or sternal wire placement.\(^9\)

*The Remi group exhibited significantly higher maximum and average pain scores during the first hour of weaning and extubation, and the Remi group had more patients complain of nausea, wound pain, and suboptimum pain therapy.\(^9\)

**Continuous infusions of Remi should be administered only by an infusion device and continuous monitoring is necessary. Interruption of infusion will result in rapid offset of effect.\(^1\)

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> “…rapid postoperative awakening, quicker recovery and earlier neurological examination suggest that remifentanil-desflurane is a suitable alternative to fentanyl-desflurane as a general anaesthetic for patients undergoing carotid artery surgery.”\(^2\)

The value of Remifentanil

**Craniotomy**

- **Rapid response** to dose adjustment (5 to 10 minutes) for predictable control of analgesic coverage.
- **Maintains hemodynamic stability** in intracranial surgery.
- **No effect** on cerebrovascular reactivity to CO₂ or intracranial pressure.
- **Rapid offset and recovery** with no accumulation regardless of infusion duration.
- **Rapid awakening and emergence** for neurological assessment.

Within 5 to 10 minutes after discontinuation of Remi, no residual analgesic activity will be present. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Other analgesics should be administered prior to discontinuation of Remi where postoperative pain is anticipated.

**Spinal fusion**

- **Rapid response** to dose titration for rapid transition to a wake-up test.
- **Provides confidence** in accurate neuromonitoring.
- **Maintains hemodynamic stability** in spinal surgery.
- **Rapid offset and recovery** with no accumulation regardless of infusion duration.
- **Rapid awakening and emergence** for neurological assessment.

Normal recovery score at 30 minutes was achieved by 81% of Remi patients versus 61% of fentanyl patients. Recovery rates were similar at 45 minutes.

Despite the need for close titration and higher risk of treatable postoperative hypertension, propofol-Remi allowed for earlier cognitive recovery.

Remi is contraindicated for epidural or intrathecal administration.

The quality of the wake-up test was not significantly better in Remi-treated patients.

Authors note that the advantages of using Remi must be balanced against increased costs and the need for vigilant control of postoperative pain.

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“Remifentanil may be useful in neuroanesthesia because of its ultra-short duration of action allowing a more predictable emergence and recovery.”


“...both remifentanil and fentanyl infusion during balanced anesthesia allow satisfactory monitoring of SSEPs. Remifentanil infusion offers the advantage of quicker recovery from anesthesia and less variability in SSEPs morphology.”

The value of Remifentanil

Functional endoscopic sinus surgery (FESS)

- Helps improve surgical conditions and reduces bleeding to improve surgical visibility when included as part of TIVA\(^{18,19}\)
- Can help achieve deliberate hypotension\(^{118^*}\)
- Rapid response allows for rapid adjustment of depth of analgesia\(^{1}\)
- Helps suppress coughing without prolonging recovery\(^{20^9}\)
- Rapid recovery after discontinuation with no accumulation regardless of infusion duration\(^{1}\)

Within 5 to 10 minutes after discontinuation of Remi, no residual analgesic activity will be present. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Other analgesics should be administered prior to discontinuation of Remi where postoperative pain is anticipated.

\(^{*}\)Compared with balanced anesthesia, Remi may result in hypotension.\(^{18}\)
\(^{1}\)Respiratory depression, apnea, tachycardia, bradycardia, hypotension, and hypertension have been reported with Remi as adverse events.\(^{1}\)
\(^{9}\)Continuous infusions of Remi should be administered only by an infusion device and continuous monitoring is necessary. Interruption of infusion will result in rapid offset of effect.\(^{1}\)

“INTRAVENOUS ANESTHESIA USING PROPOFOL-REMIFENTANIL PROVIDES BETTER SURGICAL CONDITIONS COMPARED WITH A TRADITIONAL BALANCED ANESTHESIA TECHNIQUE USING ISOFLURANE-ALFENTANIL.”\(^{19}\)


Bariatric surgery

- No accumulation in adipose tissue\(^{1,4}\)
- No difference in pharmacokinetics in nonobese vs obese\(^{6}\) patients when normalized to ideal body weight (IBW)\(^{#1,21}\)
- Pharmacokinetics and pharmacodynamics are not altered in hepatic and renal impairment\(^{1}\)
- Rapid response allows for rapid adjustment of depth of analgesia\(^{1}\)
- Rapid recovery to help facilitate early extubation in gastric bypass surgery\(^{22^*,23^††}\)
- Remi should be used with caution in obese patients

\(^{3}\)Study design used Remi in conjunction with propofol. Remi infusions were discontinued after extubation. Authors noted a dose-dependent cough suppression during emergence without impact on recovery.\(^{20}\)
\(^{4}\)Clearance of Remi generally correlates with total body weight and may vary in morbidly obese patients due to variation in physiology and pharmacodynamics.\(^{1}\)
\(^{5}\)In obese patients (greater than 30% over their IBW), dosing should be based on IBW.
\(^{*}\)During the first 4 hours of recovery, pain was reported higher in the Remi group. Duration of stay in the postanesthesia care unit was comparable between sufentanil and Remi.\(^{22}\)
\(^{††}\)Postoperative pain and PONV were higher in the Remi group.\(^{23}\)

“TIVA WITH MIDAZOLAM, REMIFENTANIL, PROPOFOL AND CISATRACURIUM WAS FOUND TO BE EFFECTIVE, SECURE, PREDICTABLE AND ECONOMIC FOR THE ANESTHETIC MANAGEMENT OF MORBIDLY OBESIE PATIENTS.”\(^{24}\)

IMPORTANT RISK INFORMATION
(continued from front)

Vital signs and oxygenation must be continuously monitored during ULTIVA® (remifentanil HCl) for Injection administration. ULTIVA produces adverse events that are characteristic of μ-opioids, such as respiratory depression, apnea, tachycardia, bradycardia, hypotension, hypertension, and skeletal muscle (including chest wall) rigidity. Because these effects are dose-dependent and can occur rapidly, continuous monitoring is necessary. ULTIVA 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.

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.

ULTIVA should be used with caution in pediatric, geriatric, and morbidly obese patients due to high variability in pharmacodynamics and dose/response. Intraoperative awareness has been reported with concomitant administration with propofol infusion ≤75 mcg/kg/min.

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.

In nonintubated 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 (within 5 to 10 min) upon discontinuation of ULTIVA at recommended doses. Discontinuation of an infusion of ULTIVA should be preceded by the establishment of adequate postoperative analgesia particularly where postoperative pain is anticipated.

ULTIVA SHOULD BE USED IN CAREFULLY MONITORED SETTINGS BY SPECIFICALLY TRAINED PERSONS NOT INVOLVED IN THE SURGICAL OR DIAGNOSTIC PROCEDURE. OXYGEN SATURATION IS TO BE CONTINUOUSLY MONITORED. RESUSCITATIVE AND INTUBATION EQUIPMENT, OXYGEN, AND AN OPIOID ANTAGONIST MUST BE READILY AVAILABLE.

The value of Remifentanil

Helping pharmacists support patient care

- Rapid response\(^1\)
- Rapid recovery\(^1\)
- Established hemodynamic profile\(^1,5\)
- Early post-op neurological assessment\(^2,15\)
- No accumulation\(^1\)

Remi produces adverse events that are characteristic of \(\mu\)-opioids, such as respiratory depression, apnea, tachycardia, bradycardia, hypotension, hypertension, and skeletal muscle (including chest wall) rigidity.

\(^1\)Continuous infusions of Remi should be administered only by an infusion device and continuous monitoring is necessary. Interruption of infusion will result in rapid offset of effect.\(^1\)

\(^2\)Within 5 to 10 minutes after discontinuation of Remi, no residual analgesic activity will be present. However, respiratory depression may occur in some patients up to 30 minutes after termination of infusion due to residual effects of concomitant anesthetics. Other analgesics should be administered prior to discontinuation of Remi where postoperative pain is anticipated.\(^1\)

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