Remifentanil—
Addressing the analgesic challenges of ambulatory plastic surgery¹-⁴

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 pages 10-11, and accompanying full Prescribing Information in pocket for all precautions, warnings, contraindications, and adverse events.
Predictable control\textsuperscript{1-4}

**Rapid response**
- Allows for rapid titration to help control intraoperative pain and hemodynamics\textsuperscript{**1,3,4**}

**Rapid recovery**
- Results in less postoperative nausea and vomiting than fentanyl 2-12 hours following plastic surgery\textsuperscript{**4**}

**Added characteristics of Remifentanil**
- Well-established hemodynamic profile\textsuperscript{1,4,5,6}
- No accumulation regardless of infusion duration\textsuperscript{1}
- Can be used in patients with renal or hepatic impairment\textsuperscript{1}

Remi\textsuperscript{**} 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.

\*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.\textsuperscript{1}

\textsuperscript{1}In premedicated patients undergoing anesthesia, 1-minute infusions of \(<2\ mcg/kg\) of Remi cause dose-dependent hypotension and bradycardia. When appropriate, bradycardia and hypotension can be reversed by reduction of the rate of infusion of Remi or the dose of concurrent anesthetics, or by the administration of fluids or vaspressors. Tachycardia and hypertension have also been reported.\textsuperscript{1}

\textsuperscript{2}In patients undergoing upper and lower eyelid blepharoplasty or otoplasty under local anesthesia.\textsuperscript{3}

\textsuperscript{3}Study evaluated 40 patients undergoing septrhinoplasty randomized to receive desflurane-Remi or total intravenous anesthesia including Remi. Hemodynamic parameters were not significantly different between groups.\textsuperscript{4}

\textsuperscript{4}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.\textsuperscript{1}

\textsuperscript{5}No significant differences were found between fentanyl and Remi 0-2 hours or 12-24 hours postop.\textsuperscript{2} In general anesthesia studies of adults given Remi (\(n = 281\)), 22% experienced nausea and 8% experienced vomiting.\textsuperscript{3}

**Facial plastic surgery case study**

63-year-old female
- 5’8”, 65.8 kg (145 lb)
- BMI 22.0 kg/m\textsuperscript{2}

**Comorbidities**
- Hypertension
- Postmenopausal
- Smoker

**Previous hysterectomy for adenocarcinoma**

**Uses herbal supplements**

This case study is for illustrative and educational purposes only. The dosing regimen is specific to this case study and other regimens may vary depending on patient and procedure. Any use of this product is subject to the judgment of the practitioner in each case. Please consult the full Prescribing Information in the use of this product.

**Procedural considerations**
- Anesthesia goals include a clear surgical field, lack of patient movement, nonstimulating emergence from anesthesia, rapid return of consciousness and protective airway reflexes, prevention of PONV, and fast-tracking patients for discharge.\textsuperscript{7}

**Patient considerations**
- Patients >60 years are at increased risk for intraoperative bleeding and postoperative bruising.\textsuperscript{8,9}
- Smokers are at increased risk of perioperative complications and smoking cessation is recommended 4 weeks preoperatively and 2 weeks postoperatively.\textsuperscript{10}
- Postmenopausal hypertension increases cardiovascular risk\textsuperscript{11} and systemic hypertension may predispose patients to hematoma formation.\textsuperscript{7}
- Herbal supplements may increase risk of perioperative bleeding and should be discontinued at least 36 hours to 7 days prior to surgery.\textsuperscript{12}

PONV = postoperative nausea and vomiting.

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## Hypothetical total intravenous anesthesia (TIVA) plan

<table>
<thead>
<tr>
<th>Stage of procedure</th>
<th>Action</th>
<th>Notes and safety considerations</th>
</tr>
</thead>
</table>
| **Preoperative**   | Continue antihypertensives  
Perphenazine 4 mg po  
Acetaminophen 1000 mg po  
Glycopyrrolate 0.2 mg IV prior to induction | • 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. Due to the presence of glycine in the formulation, Remi is contraindicated for epidural or intrathecal administration and in patients with known hypersensitivity to fentanyl analogs¹ |
| **Induction**      | Propofol 1-2 mg/kg IV  
Remi* 2 mcg/kg/min IV over 1 minute followed by 0.2-0.5 mcg/kg/min adjusted to hemodynamic response  
Rocuronium 0.6 mg/kg IV  
Dexamethasone 4 mg IV | • Remi has a synergistic effect with other anesthesia drugs and may reduce the dosage of propofol and other agents¹  
• Administer Remi in port closest to patient to avoid accumulation in IV tubing. Titrate slowly in small increments until patient response is adequate to help minimize side effects, such as muscle rigidity or respiratory depression. Vital signs and oxygen saturation must be continuously monitored during Remi administration¹  
• Intraoperative awareness has been reported with concomitant administration of Remi with propofol infusion ≤75 mcg/kg/min¹ |
| **Maintenance**    | Propofol adjusted to maintain BIS between 40-60 (~75-150 mcg/kg/min IV)  
Prepare for management of potential consequences of vasoactive agents  
Remi 0.2-0.5 mcg/kg/min IV based on hemodynamic response and additional boluses of 1 mcg/kg over 1 minute as needed prior to osteotomy  
Ondansetron 4 mg IV – 30 minutes before conclusion | • Increase dose of Remi for painful or stimulating parts of procedure. Rapid response within 5-10 minutes of dose adjustment¹  
• Maintain adequate amount of analgesic to prevent increase in blood pressure. Adjust dose of Remi to help provide hemodynamic stability¹  
• Prepare for postoperative pain. Rapid offset of Remi results in rapid dissipation of analgesic effect within 5-10 minutes of discontinuation. Other analgesics should be administered prior to discontinuation where postoperative pain is anticipated¹  
• Rapid offset and rapid recovery regardless of infusion duration¹  
• Due to residual effects of concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of Remi¹  
• In adult general anesthesia studies of 281 patients given Remi for postoperative analgesia, 61 (22%) experienced nausea, 22 (8%) experienced vomiting, 19 (7%) experienced respiratory depression, and 15 (5%) experienced shivering. After discontinuation in 929 patients, 339 (36%) experienced nausea, 150 (16%) experienced vomiting, 49 (5%) experienced shivering, and 44 (5%) experienced fever¹ |
| **Emergence and postoperative** | Administer appropriate selection of anesthetic block or pain relief agent for postoperative pain  
Clear airway of secretions and blood, and place orogastric tube to suction stomach  
Concomitantly discontinue propofol  
Reduce Remi to 0.05 mcg/kg/min IV at time of dressing placement  
Extubate as appropriate and discontinue Remi | **Please see full Prescribing Information in pocket for dosing and administration.** |

*Remifentanil is commonly referred to as Remi by anesthesia providers.
# Remifentanil case approach

## Hypothetical IV and inhalational (balanced) plan

<table>
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<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td>Continue antihypertensives</td>
<td>• Remifentanil* 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. Due to the presence of glycine in the formulation, Remifentanil is contraindicated for epidural or intrathecal administration and in patients with known hypersensitivity to fentanyl analogs.</td>
</tr>
<tr>
<td></td>
<td>Perphenazine 4 mg po</td>
<td>• Remifentanil has a synergistic effect with other anesthesia drugs and may reduce the dosage of propofol and other agents.</td>
</tr>
<tr>
<td></td>
<td>Acetaminophen 1000 mg po</td>
<td>• Administer Remifentanil in port closest to patient to avoid accumulation in IV tubing. Titrated slowly in small increments until patient response is adequate to help minimize side effects, such as muscle rigidity or respiratory depression. Vital signs and oxygen saturation must be continuously monitored during Remifentanil administration.</td>
</tr>
<tr>
<td></td>
<td>Glycopyrrolate 0.2 mg IV prior to induction</td>
<td>• Intraoperative awareness has been reported with concomitant administration of Remifentanil with propofol infusion ≤75 mcg/kg/min.</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>Propofol 1-2 mg/kg IV</td>
<td>• Increase dose of Remifentanil for painful or stimulating parts of procedure. Rapid offset and recovery within 5-10 minutes of dose adjustment.</td>
</tr>
<tr>
<td></td>
<td>Remifentanil* 2 mcg/kg/min IV over 1 minute followed by</td>
<td>• Maintain adequate amount of analgesic to prevent increase in blood pressure. Adjust dose of Remifentanil to help provide hemodynamic stability.</td>
</tr>
<tr>
<td></td>
<td>0.2-0.5 mcg/kg/min IV adjusted to hemodynamic response</td>
<td>• Prepare for postoperative pain. Rapid offset of Remifentanil results in rapid dissipation of analgesic effect within 5-10 minutes of discontinuation. Other analgesics should be administered prior to discontinuation where postoperative pain is anticipated.</td>
</tr>
<tr>
<td></td>
<td>Rocuronium 0.6 mg/kg IV</td>
<td>• Rapid offset and rapid recovery regardless of infusion duration.</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 4 mg IV</td>
<td>• Due to residual effects of concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of Remifentanil.</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Nitrous oxide 70% and sevoflurane 0.5%-1.5% adjusted to maintain BIS</td>
<td>• In adult general anesthesia studies of 281 patients given Remifentanil for postoperative analgesia, 61 (22%) experienced nausea, 22 (8%) experienced vomiting, 19 (7%) experienced respiratory depression, and 15 (5%) experienced shivering. After discontinuation in 929 patients, 339 (36%) experienced nausea, 150 (16%) experienced vomiting, 49 (5%) experienced shivering, and 44 (5%) experienced fever.</td>
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<td>between 40-60</td>
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<td>Prepare for management of potential consequences of vasoactive agents</td>
<td>• Maintain adequate amount of analgesic to prevent increase in blood pressure. Adjust dose of Remifentanil to help provide hemodynamic stability.</td>
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<td></td>
<td>Remifentanil 0.2-0.5 mcg/kg/min IV based on hemodynamic response</td>
<td>• Prepare for postoperative pain. Rapid offset of Remifentanil results in rapid dissipation of analgesic effect within 5-10 minutes of discontinuation. Other analgesics should be administered prior to discontinuation where postoperative pain is anticipated.</td>
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<td>additional boluses of 1 mcg/kg over 1 minute as needed prior to</td>
<td>• Rapid offset and rapid recovery regardless of infusion duration.</td>
</tr>
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<td></td>
<td>osteotomies</td>
<td>• Due to residual effects of concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of Remifentanil.</td>
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<td>Ondansetron 4 mg IV –30 minutes before conclusion</td>
<td>• In adult general anesthesia studies of 281 patients given Remifentanil for postoperative analgesia, 61 (22%) experienced nausea, 22 (8%) experienced vomiting, 19 (7%) experienced respiratory depression, and 15 (5%) experienced shivering. After discontinuation in 929 patients, 339 (36%) experienced nausea, 150 (16%) experienced vomiting, 49 (5%) experienced shivering, and 44 (5%) experienced fever.</td>
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<td><strong>Emergence and</strong></td>
<td>Discontinue volatile agent 15 minutes prior to end of case</td>
<td>• Prepare for postoperative pain. Rapid offset of Remifentanil results in rapid dissipation of analgesic effect within 5-10 minutes of discontinuation. Other analgesics should be administered prior to discontinuation where postoperative pain is anticipated.</td>
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<td>postoperative**</td>
<td>Administer appropriate selection of anesthetic block or pain relief</td>
<td>• Rapid offset and rapid recovery regardless of infusion duration.</td>
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<td></td>
<td>agent for postoperative pain</td>
<td>• Due to residual effects of concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of Remifentanil.</td>
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<td>Clear airway of secretions and blood, and place orogastric tube to</td>
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<td>Reduce Remifentanil to 0.05 mcg/kg/min IV at time of dressing</td>
<td>• Rapid offset and rapid recovery regardless of infusion duration.</td>
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<td>placement</td>
<td>• Due to residual effects of concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of Remifentanil.</td>
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<td></td>
<td>Discontinue N₂O</td>
<td>• In adult general anesthesia studies of 281 patients given Remifentanil for postoperative analgesia, 61 (22%) experienced nausea, 22 (8%) experienced vomiting, 19 (7%) experienced respiratory depression, and 15 (5%) experienced shivering. After discontinuation in 929 patients, 339 (36%) experienced nausea, 150 (16%) experienced vomiting, 49 (5%) experienced shivering, and 44 (5%) experienced fever.</td>
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<td>Extubate as appropriate and discontinue Remifentanil</td>
<td>• Prepare for postoperative pain. Rapid offset of Remifentanil results in rapid dissipation of analgesic effect within 5-10 minutes of discontinuation. Other analgesics should be administered prior to discontinuation where postoperative pain is anticipated.</td>
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Goal: Predictable control

**Intraoperative**

- **Achieved controlled hypotension** to help reduce intraoperative bleeding during rhinoplasty \(^{13,14}\)

- **Significantly reduces intraoperative stress responses** during outpatient and ambulatory procedures \(^{15,16}\)

- **Provides a consistently stable intraoperative course compared to fentanyl** for both inpatients and outpatients \(^5\)

- Respiratory depression, apnea, tachycardia, bradycardia, hypotension, hypertension, and skeletal muscle (including chest wall) rigidity have been reported with Remi as adverse events \(^1\)

**Results in less postoperative nausea and vomiting** than fentanyl 2-12 hours following plastic surgery \(^2\)

**Recovery**

- No significant differences were found between fentanyl and Remi 0-2 hours or 12-24 hours postop. \(^2\)

- **Significantly reduces intraoperative stress responses** during outpatient and ambulatory procedures \(^{15,16}\)

- **Allows for early awakening** when used with propofol-based TIVA in ambulatory procedures \(^{16}\)

- **Provides earlier response to verbal command, discharge from the OR, and eligibility for discharge home compared to fentanyl in outpatient surgery** \(^{16}\)

\(^1\)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. \(^1\)

\(^3\)Study evaluated 200 patients undergoing ambulatory laparoscopic surgery. Significantly fewer Remi patients than alfentanil patients had any intraoperative responses or responses to trocar insertion. Remi patients qualified for Phase 1 discharge later and were given postoperative analgesics sooner than alfentanil patients. Times to awakening and actual discharge times from the ambulatory center were similar between groups. \(^16\)

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IMPORTANT RISK INFORMATION
(continued from front)

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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 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 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.

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.

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Remifentanil—
Addressing ambulatory plastic surgery analgesic challenges from surgery to recovery¹-⁴

INDICATIONS AND IMPORTANT RISK INFORMATION

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Predictable control\textsuperscript{1-4}

\begin{tabular}{ |p{15cm}| }
\hline
\textbf{Remifentanil characteristics} \\
\hline
\textbf{Provides rapid response} to titration to help control \textsuperscript{1-3}\textsuperscript{,} intraoperative pain and hemodynamics. \\
\hline
\textbf{Significantly reduces intraoperative stress responses} during outpatient and ambulatory procedures. \\
\hline
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\textsuperscript{1}Study evaluated 40 patients undergoing septorhinoplasty randomized to receive desflurane-Remi or total intravenous anesthesia including Remi. Hemodynamic parameters were not significantly different between groups.\textsuperscript{4}

\textsuperscript{1}In 201 outpatients, the Remi group experienced significantly fewer stress responses to surgical stimuli than the alfentanil group. Significantly fewer Remi patients responded to skin closure. Times to spontaneous respiration, adequate respiratory rate, and tracheal extubation were significantly shorter than alfentanil patients. Remi patients showed significantly better recovery of psychomotor and psychometric function between 30 and 90 min after surgery. Incidences of intraop hypotension and postop shivering were significantly higher with Remi.\textsuperscript{3}

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The study by Philip and colleagues (reference 6) was supported in part by Glaxo Wellcome Inc. ULTIVA is a registered trademark of Glaxo Group Limited. The Mylan logo is a registered trademark of Mylan Inc.