

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**REMIFENTANIL HYDROCHLORIDE FOR INJECTION**

1 mg / vial, 2 mg / vial, 5 mg / vial of remifentanil (as remifentanil hydrochloride)  
Lyophilized Powder for Injection  
Sterile

Opioid Component to Anesthesia

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## REMIFENTANIL HYDROCHLORIDE FOR INJECTION

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength  | Non-Medicinal Ingredients  |
|-------------------------|---|----------------------------|
| Intravenous (i.v)       | 1 mg, 2 mg, 5 mg vials of remifentanil base as the hydrochloride salt | Glycine, hydrochloric acid |

#### INDICATIONS AND CLINICAL USE

##### **Adults**

Remifentanil Hydrochloride for Injection is indicated for intravenous (i.v.) administration as an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures.

Due to insufficient safety and efficacy data, remifentanil is not recommended for use in spontaneous ventilation anesthesia, in monitored anesthesia care, for continuation as an analgesic in the immediate postoperative period, in neurosurgery, in cardiac surgery, or in pediatric anesthesia.

Remifentanil Hydrochloride for Injection is not indicated as an as-needed (prn) analgesic.

##### **Geriatrics (> 65 years of age)**

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

##### **Pediatrics (< 18 years of age)**

The safety and efficacy of Remifentanil Hydrochloride for Injection has not been studied in the pediatric population. Therefore, the use of Remifentanil Hydrochloride for Injection is not recommended in patients under 18 years of age.

#### CONTRAINDICATIONS

Due to the presence of glycine in the formulation, Remifentanil Hydrochloride for Injection is contraindicated for epidural or intrathecal administration.

- Patients who are hypersensitive to the active substance Remifentanil hydrochloride or

other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases / conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

#### Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Remifentanil Hydrochloride for Injection should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see **DOSAGE AND ADMINISTRATION**).

#### Addiction, Abuse, and Misuse

Remifentanil Hydrochloride for Injection poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Remifentanil Hydrochloride for Injection, and all patients should be monitored regularly for the development of these behaviors or conditions (see **WARNINGS AND PRECAUTIONS**). Remifentanil Hydrochloride for Injection should be stored securely to avoid theft or misuse.

#### Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Remifentanil Hydrochloride for Injection. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Remifentanil Hydrochloride for Injection or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

#### Accidental Exposure

Accidental ingestion of even one dose of Remifentanil Hydrochloride for Injection, especially by children, can result in a fatal overdose of remifentanil hydrochloride (see **DOSAGE AND ADMINISTRATION, Disposal**, for instructions on proper disposal).

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged maternal use of Remifentanyl Hydrochloride for Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

### **Interaction with Alcohol**

The co-ingestion of alcohol with Remifentanyl Hydrochloride for Injection should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

### **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of Remifentanyl Hydrochloride for Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

## **General**

Remifentanyl Hydrochloride for Injection should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Remifentanyl Hydrochloride for Injection as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of remifentanyl hydrochloride can occur at particularly high doses. A remifentanyl hydrochloride dose reduction or change in opioid may be required.

Remifentanyl is not recommended for use 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.

Continuous infusions of remifentanyl should be administered only by an infusion device. **I.V. bolus administration should only be used in intubated patients during the maintenance of general anesthesia.** For induction of anesthesia in nonintubated patients, a single dose of remifentanyl, not exceeding 1 mcg/ kg, may be administered over 30 to 60 seconds.

**Interruption of an infusion of remifentanyl 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 remifentanyl at recommended**

**doses. However, delayed respiratory depression may occur in some patients up to 30 minutes after termination of remifentanyl infusions due to residual effects of concomitant anesthetics. Discontinuation of an infusion of remifentanyl should be preceded by the establishment of adequate postoperative analgesia (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION).**

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

**Use of remifentanyl is associated with apnea and respiratory depression. Remifentanyl should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function. Resuscitative and intubation equipment, oxygen and an opioid antagonist must be readily available.**

**Remifentanyl should be administered only by persons specifically trained in the use of anesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation of patients in the age-group being treated. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.**

Skeletal muscle rigidity can be caused by remifentanyl and is related to the dose and speed of administration. Remifentanyl may cause chest wall rigidity (inability to ventilate) after single doses > 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 remifentanyl.

Muscle rigidity induced by remifentanyl 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.

Remifentanyl should not be administered into the same i.v. tubing with blood / serum / plasma due to potential inactivation by nonspecific esterases in blood products.

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

Intraoperative awareness has been reported in patients under 55 years of age when remifentanyl has been administered with propofol infusion rates of  $\leq 75$  mcg / kg / min. Therefore, propofol rates < 100 mcg / kg / min are not recommended for use with remifentanyl for total intravenous anesthesia in patients < 55 years of age.

### **Abuse and Misuse**

Like all opioids, Remifentanil Hydrochloride for Injection is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Remifentanil Hydrochloride for Injection should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Remifentanil Hydrochloride for Injection, should be used with particular care in patients with a history of alcohol and illicit / prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

### **Carcinogenesis and Mutagenesis**

See TOXICOLOGY section.

### **Cardiovascular**

Remifentanil hydrochloride administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative / hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Remifentanil Hydrochloride for Injection.

The use of Remifentanil Hydrochloride for Injection in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see **DOSAGE AND ADMINISTRATION**).

### **Dependence / Tolerance**

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Remifentanil Hydrochloride for Injection and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual

increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, <Adjustment or Reduction of Dosage>**).

### **Use in Drug and Alcohol Addiction**

Remifentanil Hydrochloride for Injection is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Remifentanil Hydrochloride for Injection; extreme caution and awareness is warranted to mitigate the risk.

### **Gastrointestinal Effects**

Remifentanil hydrochloride and other morphine-like opioids have been shown to decrease bowel motility. Remifentanil hydrochloride may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

### **Hepatic / Biliary / Pancreatic**

Remifentanil pharmacokinetic / pharmacodynamic profile is not changed in patients with severe hepatic impairment. However, these patients may be slightly more sensitive to respiratory depressant effects of remifentanil. Therefore, these patients should be closely monitored, and the dose of remifentanil titrated to individual patient need.

### **Neonatal Opioid Withdrawal Syndrome (NOWS)**

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Remifentanil Hydrochloride for Injection is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If Remifentanil Hydrochloride for Injection was used during pregnancy, special attention to NOWS is warranted.

### **Neurologic**

**Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol):** Remifentanil hydrochloride should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally active anti-emetics and other CNS



depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Remifentanil Hydrochloride for Injection is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

Remifentanil Hydrochloride for Injection should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

**Head Injury:** The respiratory depressant effects of remifentanil hydrochloride, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, remifentanil hydrochloride may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, remifentanil hydrochloride must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

### **Peri-Operative Considerations**

Remifentanil Hydrochloride for Injection is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Remifentanil Hydrochloride for Injection for at least 24 hours before the operation and Remifentanil Hydrochloride for Injection should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Remifentanyl Hydrochloride for Injection is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Remifentanyl hydrochloride and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

### **Use in Cardiovascular Surgery**

Clinical experience with remifentanyl in patients undergoing cardiac surgery is limited to coronary artery bypass graft procedures (CABG). There are insufficient data to make a dosage recommendation.

### **Use in Neurosurgery**

Due to the limited number of patients studied, there are insufficient data to make dosage recommendations.

### **Psychomotor Impairment**

Remifentanyl Hydrochloride for Injection may impair the mental and / or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of remifentanyl hydrochloride with other CNS depressants, including other opioids, phenothiazine, sedative / hypnotics and alcohol.

### **Renal**

The pharmacodynamic / pharmacokinetic profile of remifentanyl is not changed in patients with end stage renal disease (creatinine clearance < 10 mL / min). No dosage adjustment is necessary in this patient population.

In anephric patients, the half-life of the carboxylic acid metabolite increases from 90 minutes to approximately 30 hours. The metabolite is removed by hemodialysis with a dialysis extraction ratio of approximately 30%.

### **Respiratory**

**Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and

death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Remifentanil hydrochloride should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Remifentanil Hydrochloride for Injection, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Remifentanil Hydrochloride for Injection and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Remifentanil Hydrochloride for Injection are essential. Overestimating the Remifentanil Hydrochloride for Injection dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

**Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Remifentanil Hydrochloride for Injection, as in these patients, even usual therapeutic doses of Remifentanil Hydrochloride for Injection may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Remifentanil Hydrochloride for Injection is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Within 5 to 10 minutes after the discontinuation of Remifentanil Hydrochloride for Injection, 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. 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 remifentanil.

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

### **Special Populations**

**Special Risk Groups:** Remifentanil Hydrochloride for Injection should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to

debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy, or urethral stricture.

**Pregnant Women:** Studies in humans have not been conducted. Remifentanil Hydrochloride for Injection crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

**Labour, Delivery and Nursing Women:**

Since opioids can cross the placental barrier and are excreted in breast milk, Remifentanil Hydrochloride for Injection is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Remifentanil Hydrochloride for Injection is used in this population.

**Pediatrics (< 18 years of age):**

The safety and efficacy of Remifentanil Hydrochloride for Injection have not been studied in the pediatric population. Therefore, use of Remifentanil Hydrochloride for Injection is not recommended in patients under 18 years of age.

**Geriatrics (> 65 years of age):** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

The clearance of remifentanil is reduced (approximately 25%) in the elderly (> 65 years of age) compared to young adults (average 25 years of age). However, remifentanil blood concentrations fall as rapidly after termination of administration in the elderly as in young adults. The pharmacodynamic activity of remifentanil (as measured by the EC50 for development of delta waves on the electroencephalogram [EEG]) increases with increasing age. The EC50 of remifentanil for this measure was 50% less in patients over 65 years of age when compared to healthy volunteers (25 years of age); therefore, the recommended starting dose of remifentanil should be decreased by 50% in elderly patients and then titrated to individual patient need (see **DOSAGE AND ADMINISTRATION**).

**Morbidly Obese Patients**

As for all potent opioids, caution is required when used in morbidly obese patients because of alterations in cardiovascular and respiratory physiology (see **DOSAGE AND ADMINISTRATION**).

### **ASA III / IV Patients**

Limited data is available from 65 ASA III and 1 ASA IV patients. As the hemodynamic effects of potent opioids can be expected to be more pronounced in ASA III / IV patients, caution should be exercised in the administration of remifentanyl in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Remifentanyl hydrochloride produces adverse events that are characteristic of  $\mu$ -opioids, such as respiratory depression, bradycardia, hypotension, and skeletal muscle rigidity. These adverse events dissipate within minutes of discontinuing or decreasing the infusion rate of remifentanyl (see **ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS** on the management of these events).

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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.

Approximately 2,492 patients were exposed to remifentanyl in controlled clinical trials. The frequencies of adverse events during general anesthesia with the recommended doses of remifentanyl hydrochloride are given in **Table 1**.

In the elderly population (> 65 years), the incidence of hypotension is higher, whereas the incidence of nausea and vomiting is lower (see **WARNINGS AND PRECAUTIONS**).

Data from cardiac risk analysis in non-cardiac general anesthesia studies indicate the incidence of hypotension in patients with cardiac risk factors (i.e., > 65 years of age, concomitant use of cardiac medication) is higher with remifentanyl than comparator drugs (27% vs. 12%, respectively).

**Table 1**  
**Adverse Events ≥ 1% of Patients in General Anesthesia Studies**  
**at the Recommended Doses of Remifentanyl\***

| Adverse Event          | Induction / Maintenance   |                                       | After Discontinuation     |                                       |
|------------------------|---------------------------|---------------------------------------|---------------------------|---------------------------------------|
|                        | Remifentanyl<br>(n = 921) | Alfentanil /<br>Fentanyl<br>(n = 466) | Remifentanyl<br>(n = 929) | Alfentanil /<br>Fentanyl<br>(n = 466) |
| Nausea                 | 8 (<1%)                   | 0                                     | 339 (36%)                 | 202 (43%)                             |
| Hypotension            | 178 (19%)                 | 30 (6%)                               | 16 (2%)                   | 9 (2%)                                |
| Vomiting               | 4 (<1%)                   | 1 (<1%)                               | 150 (16%)                 | 91 (20%)                              |
| Muscle rigidity        | 98 (11%)**                | 37 (8%)                               | 2 (<1%)                   | 1 (<1%)                               |
| Bradycardia            | 62 (7%)                   | 24 (5%)                               | 11 (1%)                   | 6 (1%)                                |
| Shivering              | 3 (<1%)                   | 0                                     | 49 (5%)                   | 10 (2%)                               |
| Fever                  | 1 (<1%)                   | 0                                     | 44 (5%)                   | 9 (2%)                                |
| Dizziness              | 0                         | 0                                     | 27 (3%)                   | 9 (2%)                                |
| Visual disturbance     | 0                         | 0                                     | 24 (3%)                   | 14 (3%)                               |
| Headache               | 0                         | 0                                     | 21 (2%)                   | 8 (2%)                                |
| Respiratory depression | 1 (<1%)                   | 0                                     | 17 (2%)                   | 20 (4%)                               |
| Apnea                  | 0                         | 1 (<1%)                               | 2 (<1%)                   | 1 (<1%)                               |
| Pruritis               | 2 (<1%)                   | 0                                     | 22 (2%)                   | 7 (2%)                                |
| Tachycardia            | 6 (<1%)                   | 7 (2%)                                | 10 (1%)                   | 8 (2%)                                |
| Postoperative pain     | 0                         | 0                                     | 4 (<1%)                   | 5 (1%)                                |
| Hypertension           | 10 (1%)                   | 7 (2%)                                | 12 (1%)                   | 8 (2%)                                |
| Agitation              | 2 (<1%)                   | 0                                     | 6 (<1%)                   | 1 (<1%)                               |
| Hypoxia                | 0                         | 0                                     | 10 (1%)                   | 7 (2%)                                |

\* **Not all doses of remifentanyl were equipotent to the comparator opioid. Administration of remifentanyl in excess of the recommended dose (i.e., doses >1 and up to 20 mcg / kg) resulted in a higher incidence of some adverse events: muscle rigidity (37%), bradycardia (12%), hypertension (4%), and tachycardia (4%).**

\*\* Included in the muscle rigidity incidence is chest wall rigidity (5%). The overall muscle rigidity incidence is reduced to <1% when remifentanyl is administered concurrently with or after a hypnotic induction agent.

**Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

**Nausea and Vomiting:** Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation

of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

**Constipation:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in Remifentanil Hydrochloride for Injection clinical trials, whether related or not to remifentanil hydrochloride.

#### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Other adverse events reported less frequently (<1%) include constipation and sedation.

#### **Post-Market Adverse Drug Reactions**

Very rarely, allergic reactions including anaphylaxis have been reported in patients receiving remifentanil hydrochloride in conjunction with one or more anesthetic agents.

Cough as an adverse event induced by fentanyl, sufentanil, remifentanil and alfentanil is documented in the literature.

Post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome following the concomitant use of remifentanil with a serotonergic drug, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor (see also **DRUG INTERACTIONS**).

### **DRUG INTERACTIONS**

#### **Overview**

#### **Drug-Drug Interactions**

Remifentanil clearance is not altered by concomitant administration of thiopental, isoflurane, propofol or temazepam during anesthesia. *In vitro* studies with atracurium, mivacurium, esmolol, echothiophate, neostigmine, physostigmine and midazolam revealed no inhibition of remifentanil

hydrolysis in whole human blood by these drugs. In animals the duration of muscle paralysis from succinylcholine is not prolonged by remifentanil.

Remifentanil is synergistic with other anesthetics and doses of thiopental, propofol, isoflurane and midazolam have been reduced by up to 75% with the co-administration of remifentanil. If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.

#### **Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants :**

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives / hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). Remifentanil Hydrochloride for Injection should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

#### **Serotonergic Drugs**

Coadministration of remifentanil with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition. (See also **ADVERSE REACTIONS**)

#### **Drug-Lifestyle Interactions**

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

### **DOSAGE AND ADMINISTRATION**

#### **Dosing Considerations**

Due to insufficient safety and efficacy data, Remifentanil Hydrochloride for Injection is not recommended for use in spontaneous ventilation anesthesia, in monitored anesthesia care, for continuation as an analgesic in the immediate postoperative period, in neurosurgery, in cardiac surgery, or in pediatric anesthesia.

Remifentanil 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.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.



### **Recommended Dose and Dosage Adjustment**

Remifentanil is synergistic with other anesthetics and doses of thiopental, propofol, isoflurane and midazolam have been reduced by up to 75% with the co-administration of remifentanil. At the recommended doses shown in **Table 2**, remifentanil significantly reduces the amount of hypnotic agent required to maintain anesthesia. Therefore, isoflurane and propofol should be administered as recommended below to avoid excessive depth of anesthesia.

Intraoperative awareness has been reported in patients under 55 years of age when remifentanil has been administered with propofol infusion rates of  $\leq 75$  mcg / kg / min. Therefore, propofol rates  $<100$  mcg / kg / min are not recommended for use with remifentanil for total intravenous anesthesia in patients  $< 55$  years of age.

I.V. bolus administration should only be used in intubated patients during the maintenance of general anesthesia. For induction of anesthesia in nonintubated patients, a single dose of remifentanil, not exceeding 1 mcg / kg, may be administered over 30 to 60 seconds.

Reconstituted solutions of remifentanil should be diluted prior to administration (see **DOSAGE AND ADMINISTRATION, Reconstitution, Parenteral Products**).

The administration of remifentanil must be individualized based on the patient's response. **Table 2** summarizes the recommended doses in adult patients, predominately ASA physical status I, II, or III.

| <b>Table 2<br/>Dosing Guidelines</b>                                       |  |   |  |
|--|--|---|--|
| <b>Phase</b>   | <b>Continuous i.v. Infusion of Remifentanil Hydrochloride for Injection (mcg / kg / min)</b> | <b>Infusion Dose Range of Remifentanil Hydrochloride for Injection (mcg / kg / min)</b> | <b>Supplemental i.v. Bolus Dose of Remifentanil Hydrochloride for Injection (mcg / kg)</b> |
| <b>Induction of Anesthesia</b><br>(through intubation)                     | 0.5 - 1†   |   |  |
| <b>Maintenance of anesthesia with:</b>                                     |  |   |  |
| Nitrous oxide (66%)  | 0.4  | 0.1-2   | 0.5-1  |
| Isoflurane (starting dose 0.5 MAC)   | 0.25   | 0.05-2  | 0.5-1  |
| Propofol (starting dose 100 mcg / kg / min)                                | 0.25   | 0.05-2  | 0.5-1  |
| † An initial dose of 1 mcg / kg may be administered over 30 to 60 seconds. |  |   |  |

### **During Induction of Anesthesia**

Remifentanil 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 remifentanil, 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 remifentanyl should be decreased in accordance with the dosing guidelines in **Table 2**. Due to the fast onset and short duration of action of remifentanyl, the rate of administration during anesthesia can be titrated upward in 25% to 100% increments or downward in 25% to 50% decrements every 2 to 5 minutes to attain the desired level of  $\mu$ -opioid effect. In response to light anesthesia or transient episodes of intense surgical stress, supplemental bolus doses of 0.5 to 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.

### **Guidelines for Discontinuation**

**Upon discontinuation of remifentanyl, the i.v. tubing should be cleared to prevent the inadvertent administration of remifentanyl at a later time. Due to the rapid offset of action of remifentanyl, no residual analgesic activity will be present within 5 to 10 minutes after discontinuation. 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 those patients undergoing surgical procedures where postoperative pain is generally anticipated, alternative analgesics should be administered prior to discontinuation of remifentanyl. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of follow-up care.**

### **Use in Elderly Patients**

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Due to the increased sensitivity to the pharmacological effects of remifentanyl in this population (> 65 years), the starting doses of remifentanyl should be decreased by 50% and then be titrated to individual patient need (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

### **Use in Obese Patients**

The starting doses of remifentanyl should be based on ideal body weight in obese patients as the clearance and volume of distribution of remifentanyl are better correlated with ideal body weight than actual body weight in this population.

### **Preanesthetic Medication**

The need for premedication and the choice of anesthetic agents must be individualized. In clinical studies, patients who received remifentanyl frequently received a benzodiazepine premedication.

### **Individualization of Infusion Rates**

Infusion rates of Remifentanyl Hydrochloride for Injection can be individualized for each patient using **Table 3**.

| <b>Table 3</b>  |   |                    |                     |
|---|---|--------------------|---------------------|
| <b>Infusion Rates of Remifentanyl Hydrochloride for Injection (mL / kg / h)</b> |   |                    |                     |
| <b>Drug Delivery Rate<br/>(mcg / kg / min)</b>                                  | <b>Infusion Delivery Rate (mL / kg / h)</b> |                    |                     |
|   | <b>25 mcg / mL</b>                          | <b>50 mcg / mL</b> | <b>250 mcg / mL</b> |
| 0.05  | 0.12  | 0.06               | 0.012               |
| 0.075   | 0.18  | 0.09               | 0.018               |
| 0.1   | 0.24  | 0.12               | 0.024               |
| 0.15  | 0.36  | 0.18               | 0.036               |
| 0.2   | 0.48  | 0.24               | 0.048               |
| 0.25  | 0.6   | 0.3                | 0.06                |
| 0.5   | 1.2   | 0.6                | 0.12                |
| 0.75  | 1.8   | 0.9                | 0.18                |
| 1.0   | 2.4   | 1.2                | 0.24                |
| 1.25  | 3.0   | 1.5                | 0.3                 |
| 1.5   | 3.6   | 1.8                | 0.36                |
| 1.75  | 4.2   | 2.1                | 0.42                |
| 2.0   | 4.8   | 2.4                | 0.48                |

**Table 4** is a guideline for milliliter-per-hour delivery for a solution of 25 mcg / mL with an infusion device.

| <b>Table 4</b>  |                            |      |      |      |      |      |      |      |
|---|----------------------------|------|------|------|------|------|------|------|
| <b>Infusion Rates of Remifentanyl Hydrochloride for Injection (mL / h) for a 25-mcg / mL Solution</b> |                            |      |      |      |      |      |      |      |
| <b>Infusion Rate (mcg / kg / min)</b>   | <b>Patient Weight (kg)</b> |      |      |      |      |      |      |      |
|   | 30                         | 40   | 50   | 60   | 70   | 80   | 90   | 100  |
| 0.05  | 3.6                        | 4.8  | 6.0  | 7.2  | 8.4  | 9.6  | 10.8 | 12.0 |
| 0.075   | 5.4                        | 7.2  | 9.0  | 10.8 | 12.6 | 14.4 | 16.2 | 18.0 |
| 0.1   | 7.2                        | 9.6  | 12.0 | 14.4 | 16.8 | 19.2 | 21.6 | 24.0 |
| 0.15  | 10.8                       | 14.4 | 18.0 | 21.6 | 25.2 | 28.8 | 32.4 | 36.0 |
| 0.2   | 14.4                       | 19.2 | 24.0 | 28.8 | 33.6 | 38.4 | 43.2 | 48.0 |

**Table 5** is a guideline for milliliter-per-hour delivery for a solution of 50 mcg / mL with an infusion device.

| <b>Table 5</b>  |                            |      |       |       |       |       |       |       |
|---|----------------------------|------|-------|-------|-------|-------|-------|-------|
| <b>Infusion Rates of Remifentanyl Hydrochloride for Injection (mL / h) for a 50-mcg / mL Solution</b> |                            |      |       |       |       |       |       |       |
| <b>Infusion Rate (mcg / kg / min)</b>   | <b>Patient Weight (kg)</b> |      |       |       |       |       |       |       |
|   | 30                         | 40   | 50    | 60    | 70    | 80    | 90    | 100   |
| 0.05  | 1.8                        | 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 6** is a guideline for milliliter-per-hour delivery for a solution of 250 mcg / mL with an infusion device.

| <b>Table 6</b>   |                            |       |       |       |       |       |       |       |
|--|----------------------------|-------|-------|-------|-------|-------|-------|-------|
| <b>Infusion Rates of Remifentanyl Hydrochloride for Injection (mL / h) for a 250-mcg / mL Solution</b> |                            |       |       |       |       |       |       |       |
| <b>Infusion Rate (mcg / kg / min)</b>  | <b>Patient Weight (kg)</b> |       |       |       |       |       |       |       |
|  | 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 |

## Physical Dependence

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Remifentanil Hydrochloride for Injection. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and / or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

## Administration

Remifentanil should be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function. Resuscitative and intubation equipment, oxygen and an opioid antagonist must be readily available.

Remifentanil should only be administered by persons specifically trained in the use of anesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation of patients in the age-group being treated. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

**Remifentanil is for i.v. use only and must not be administered by epidural or intrathecal injection. Continuous infusions of remifentanil should be administered only by an infusion device. The injection site should be close to the venous cannula and all i.v. tubing should be cleared at the time of discontinuation of infusion.**

## Reconstitution:

### Parenteral Products:

#### 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. Remifentanil Hydrochloride for Injection should be reconstituted and diluted to a recommended final concentration of 25, 50, or 250 mcg / mL prior to administration as indicated in **Table 7** and **Table 8** below.

#### **Remifentanil Hydrochloride for Injection should not be administered without dilution.**

Remifentanil Hydrochloride for Injection does not contain any antimicrobial preservatives and thus care must be taken to assure the sterility of prepared solutions.

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, colourless liquid after reconstitution and free of visible particulate matter.

Remifentanil Hydrochloride for Injection can be reconstituted and diluted to concentrations of 20 to 250 mcg / mL in any of the following i.v. fluids:

- 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
- Lactated Ringer's Injection, USP

Remifentanil Hydrochloride for Injection has been shown to be compatible with these i.v. fluids when co-administered into a running i.v. administration set.

| <b>Vial Size<br/>(mg of remifentanil base)</b> | <b>Volume of<br/>Diluent to be<br/>Added to Vial</b> | <b>Approximate*<br/>Available<br/>Volume</b> | <b>Nominal<br/>Concentration</b> |
|--|--|--|----------------------------------|
| 1 mg   | 1 mL   | 1 mL   | 1 mg / mL                        |
| 2 mg   | 2 mL   | 2 mL   | 1 mg / mL                        |
| 5 mg   | 5 mL   | 5 mL   | 1 mg / mL                        |

\* Densities for water and reconstituted Remifentanil Hydrochloride for Injection are not significantly different

**Table 8  
Dilution of Remifentanil Hydrochloride for Injection**

| <b>Final Concentration</b> | <b>Amount of remifentanil in Each Vial</b> | <b>Volume to be Added to Dilute*</b> | <b>Final Volume after Dilution</b> |
|----------------------------|--|--------------------------------------|------------------------------------|
| 25 mcg / mL                | 1 mg                                       | 39 mL                                | 40 mL                              |
|                            | 2 mg                                       | 78 mL                                | 80 mL                              |
|                            | 5 mg                                       | 195 mL                               | 200 mL                             |
| 50 mcg / mL                | 1 mg                                       | 19 mL                                | 20 mL                              |
|                            | 2 mg                                       | 38 mL                                | 40 mL                              |
|                            | 5 mg                                       | 95 mL                                | 100 mL                             |
| 250 mcg / mL               | 5 mg                                       | 15 mL                                | 20 mL                              |

\* note amounts indicated are those to be added after Remifentanil Hydrochloride for Injection has been reconstituted to a 1 mg / mL solution as indicated in Table 7 above.

### **Compatibility With Other Therapeutic Agents**

Remifentanil Hydrochloride for Injection has been shown to be compatible with Propofol Injection when coadministered into a running i.v. administration set. The compatibility of Remifentanil Hydrochloride for Injection 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 Remifentanil Hydrochloride for Injection into the same i.v. tubing with blood / serum / plasma 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, colourless liquid after reconstitution and free of visible particulate matter.

### **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional poison control centre.

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

In case of overdose or suspected overdose, discontinue administration of remifentanil, 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  $\mu$ -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 following overdose with remifentanil is not expected to last longer than the opioid antagonist, naloxone. Reversal of the opioid effects may lead to acute pain and sympathetic hyperactivity.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Remifentanil hydrochloride is a  $\mu$ -opioid agonist with rapid onset and peak effect, and ultra-short duration of action. The  $\mu$ -opioid activity of remifentanil is antagonized by opioid antagonists such as naloxone.

The analgesic effects of remifentanil are rapid in onset and offset. Its effects and side effects are dose dependent and similar to other  $\mu$ -opioids. Remifentanil in humans has a rapid blood-brain equilibration half-time of  $1 \pm 1$  minutes (mean  $\pm$  SD) and a rapid onset of action. The pharmacodynamic effects of remifentanil 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 remifentanil 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, remifentanil can be rapidly titrated to the desired depth of anesthesia / analgesia (e.g., as required by varying levels of intraoperative stress) by changing the continuous infusion rate or by administering an i.v. bolus injection.

### **Pharmacodynamics**

#### **Central Nervous System**

Remifentanil hydrochloride produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO<sub>2</sub> tension and to electrical stimulation.

Remifentanil hydrochloride depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Remifentanil hydrochloride causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

#### **Gastrointestinal Tract and Other Smooth Muscle**

Remifentanil hydrochloride causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and



pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

### **Cardiovascular System**

Remifentanil hydrochloride may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and / or peripheral vasodilation may include pruritus, flushing, red eyes, hyperhidrosis and / or orthostatic hypotension.

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

### **Endocrine System**

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

### **Immune System**

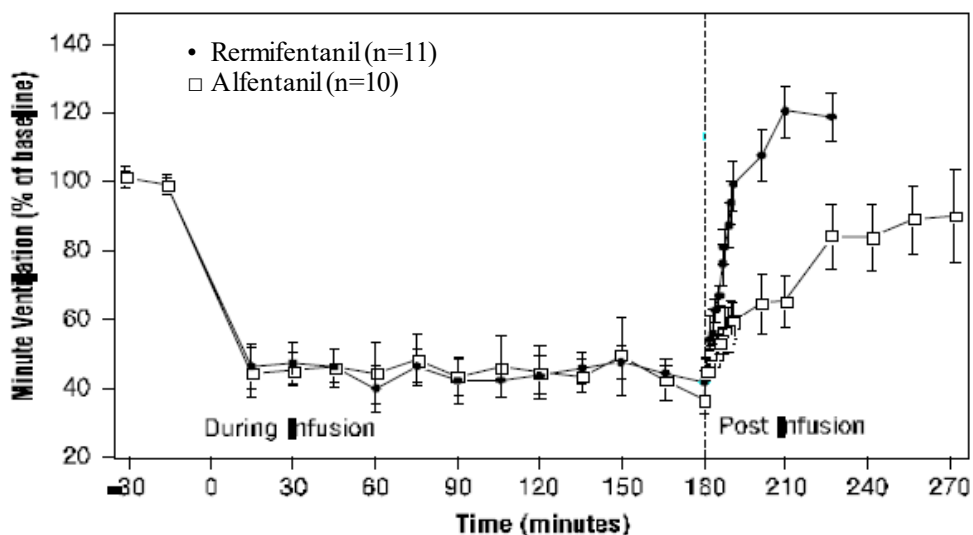
*In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

### **Haemodynamics**

In premedicated patients undergoing anesthesia, 1-minute infusions of < 2 mcg / kg of remifentanil caused 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 blood concentrations achieved. Peak hemodynamic effects occur within 3 to 5 minutes of a single dose of remifentanil or an infusion rate increase. Glycopyrrolate, atropine, and vagolytic neuromuscular blocking agents attenuate the hemodynamic effects associated with remifentanil. When appropriate, bradycardia and hypotension can be reversed by reduction of the rate of infusion of remifentanil, or the dose of concurrent anesthetics, or by the administration of fluids or vasopressors.

### **Respiration**

Remifentanil depresses respiration in a dose-related fashion. Unlike other fentanyl analogs, the duration of action of remifentanil at a given dose does not increase with increasing duration of administration, due to lack of drug accumulation. When remifentanil 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 remifentanil (see **Figure 1**).



**Figure 1: Recovery of Respiratory Drive after Equipotent\* Doses of Remifentanyl and Alfentanil Using CO<sub>2</sub>-Stimulated Minute Ventilation in Volunteers ( $\pm 1.5$  SEM)**

\*Equipotent refers to level of respiratory depression.

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

### Muscle Rigidity

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

### Anesthesia

Remifentanyl is synergistic with the activity of hypnotics (propofol and thiopental), inhaled anesthetics, and benzodiazepines (see **WARNINGS AND PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**).

### Gender

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

## **Pharmacokinetics**

### **Absorption**

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

### **Distribution**

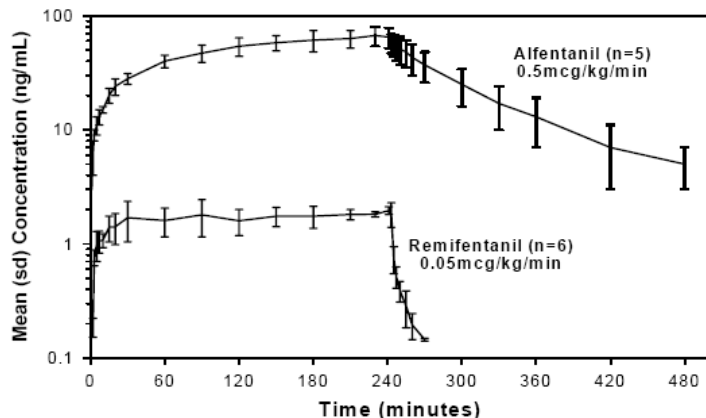
The initial volume of distribution ( $V_d$ ) of remifentanyl is approximately 100 mL / kg and represents distribution throughout the blood and rapidly perfused tissues. Remifentanyl subsequently distributes into peripheral tissues with a steady-state volume of distribution of approximately 350 mL / kg.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

### **Metabolism**

Remifentanyl is an esterase-metabolized opioid. A labile ester linkage renders this compound susceptible to hydrolysis by nonspecific esterases in blood and tissues. This hydrolysis results in production of the carboxylic acid metabolite (3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid), and represents the principal metabolic pathway for remifentanyl (> 95%). The carboxylic acid metabolite is essentially inactive (1 / 4 600 as potent as remifentanyl in dogs) and is excreted by the kidneys with an elimination half-life of approximately 90 minutes. Remifentanyl is not metabolized by plasma cholinesterase (pseudocholinesterase) and is not appreciably metabolized by the liver or lung.

### **Excretion**

The clearance of remifentanyl in young, healthy adults is approximately 40 mL / min / kg. Clearance generally correlates with total body weight (except in severely obese patients when it correlates better with ideal body weight). The high clearance of remifentanyl combined with a relatively small volume of distribution produces a short elimination half-life of approximately 3 to 10 minutes (see **Figure 2**). This value is consistent with the time taken for blood or effect site concentrations to fall by 50% (context-sensitive half-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 i.v. infusion rate will lead to a corresponding 2.5-ng / mL change in blood remifentanil concentration within 5 to 10 minutes. In intubated patients only, a more rapid increase (within 3 to 5 minutes) to a new steady state can be achieved with a 1.0-mcg / kg bolus dose in conjunction with an infusion rate increase.

### **STORAGE AND STABILITY**

Remifentanil Hydrochloride for Injection should be stored at room temperature (15°C to 30°C). Reconstituted and diluted solutions of Remifentanil Hydrochloride for Injection (20 to 250 mcg / mL) are stable for 24 hours at room temperature for all recommended i.v. fluids except those containing Lactated Ringer's Solution (stable for 4 hours).

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Remifentanil Hydrochloride for Injection is available as:

- 1 mg remifentanil base lyophilized powder in 3 mL vials (cartons of 10)
- 2 mg remifentanil base lyophilized powder in 3 mL vials (cartons of 10)
- 5 mg remifentanil base lyophilized powder in 6 mL vials (cartons of 10)

## PART II : SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

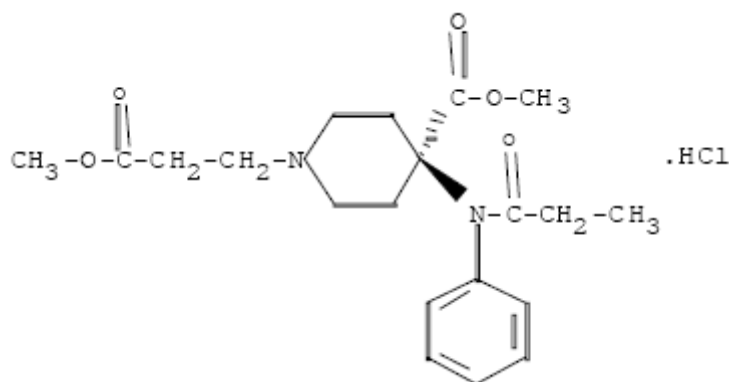
Proper name: remifentanil hydrochloride

Chemical name: 1-piperidinepropanoic acid, 4-(methoxycarbonyl)-4-[(1-oxopropyl) phenylamino]-, methyl ester, monohydrochloride

Molecular formula:  $C_{20}H_{28}N_2O_5 \cdot HCl$

Molecular mass: 412.9

Structural formula:



#### Physicochemical properties:

Physical Characteristics: White to off-white solid

pH and pKa: pH (1% solution of drug substance) is approximately 5  
pH (reconstituted i.v. solution) = 2.5-3.5  
pKa = 7.07

Melting Point: approximately 205°C

Solubility: 150 mg / mL in unbuffered water, and 5% Dextrose Injection, USP  
120 mg / mL in 0.9% Sodium Chloride Injection USP

Composition: Remifentanil Hydrochloride for Injection contains 1 mg, 2 mg or 5 mg of remifentanil base (as the hydrochloride salt) per vial. Non-medicinal ingredients include Glycine 15 mg and Hydrochloric Acid (adjust pH).

## DETAILED PHARMACOLOGY

### Animal Pharmacology

#### Pharmacodynamics

The antinociceptive properties of remifentanil were determined by rodent tail withdrawal in response to noxious radiant heat and by canine paw withdrawal in response to a noxious pinch. The potency of remifentanil seen was similar to that of alfentanil, fentanyl and sufentanil. Reversal of antinociception by naloxone confirmed that this response was opioid receptor-mediated.

Duration of antinociceptive response following intravenously administered remifentanil was dose-related and was much shorter than that of alfentanil, fentanyl, or sufentanil. Remifentanil did not accumulate with repeated or prolonged administration.

Receptor binding studies confirmed remifentanil was selective for the  $\mu$ -opioid receptor.  $EC_{50}$  values for remifentanil at  $\mu$ -,  $\delta$ -,  $\kappa$ -opioid receptors were 2.6 nM, 66 nM, and 6.1  $\mu$ M, respectively. In isolated tissues, remifentanil was a potent  $\mu$ -opioid agonist, with its actions reversed by the  $\mu$ -opioid antagonist, naltrexone, but not by the  $\delta$ - and  $\kappa$ -opioid antagonists, ICI-174864 and nor-binaltorphimine, respectively. Therefore, although remifentanil has some affinity for  $\delta$ - and  $\kappa$ -opioid receptors in binding assays, it lacks the intrinsic efficacy to produce significant activation at these receptors.

Secondary effects produced by remifentanil are characteristic for  $\mu$ -opioid agonists (consisting of dose-related bradycardia and hypotension) but are consistently shorter in duration than for other opioids. These hemodynamic effects may lessen the cardiovascular risk, and may ameliorate increased heart rate and blood pressure seen during the intraoperative stress response to surgery and anesthesia.

#### Pharmacokinetics

The propanoic acid methyl ester moiety of remifentanil is rapidly hydrolyzed by esterases in the blood and tissues to yield the carboxylic acid of remifentanil (and also the major metabolite). After infusion of remifentanil, the pharmacokinetics in dogs are linear between 0.4 mcg / kg / min and the highest rate tested 40 mcg / kg / min. The pharmacokinetics of remifentanil in beagle dogs and the metabolism and excretion of remifentanil in mice, rats, rabbits and dogs are similar to those in humans. Remifentanil does not accumulate upon repeated administration in any of the animal species studied.

Elimination is primarily through urine in all toxicological species as well as humans. The only other identified metabolite (other than the carboxylic acid of remifentanil) found in urine or feces

of mice, rats or dogs was the product of N-dealkylation on the piperidine ring. It accounted for less than 2% of the dose in all animal species.

Approximately 16-18% of the total systemic clearance of remifentanil could be accounted for in liver, kidney, blood, muscle, brain and lung. Of these, muscle contributed most to the clearance (5-9%). Liver or kidney contributed only 0-3%. This suggests that hepatic or renal insufficiency in humans should not impact greatly on remifentanil clearance.

Remifentanil was approximately 70% bound to human plasma proteins, mostly to  $\alpha$ -1-acid glycoprotein.

## TOXICOLOGY

### Acute Toxicology

Maximum Non-Lethal Doses observed in animals (and corresponding multiples of the clinical dose) seen in acute toxicology studies were:

| Species / Sex  | MNLD mg / kg | Clinical Multiple <sup>a</sup> |
|--|--------------|--------------------------------|
| Male mice  | 84           | 42,000                         |
| Female mice  | 70           | 25,000                         |
| Male rat   | 5            | 2,500                          |
| Female rat   | 7.5          | 3,750                          |
| Male and female dogs   | 80           | 40,000                         |
| <sup>a</sup> Based on the maximum recommended human bolus dose of 2 mcg / kg |              |                                |

In all studies, remifentanil produced expected signs of  $\mu$ -opioid intoxication when administered as large single bolus intravenous doses to non-ventilated mice, rats and dogs. In the rat and mouse studies, no macroscopic or microscopic changes could be attributed to administration of remifentanil. Hypoxia-induced brain microhemorrhages were observed in dogs, but these were not present in dogs killed 14 days after dosing, suggesting reversibility of this effect.

### Long-Term Toxicology

#### Subacute Toxicity Studies

| Species | Route                    | Dose                      | Duration of Study | Results  |
|---------|--------------------------|---------------------------|-------------------|--|
| Rat     | Continuous i.v. infusion | up to 5 mcg / kg / min    | 2 weeks           | ↓ food consumption and body weight gain, ↓ pancreatic acinar cell zymogen granules, ↑ serum glucose. |
|         | Bolus i.v.               | up to 2.5 mg / kg / day   | 4 weeks           | ↓ absolute and relative epididymus weight  |
| Dog     | Continous i.v. infusion  | up to 0.25 mcg / kg / min | 2 weeks           | ↓ food consumption and body weight gain  |
|         | Bolus i.v.               | up to 40 mg / kg / day*   | 4 weeks           | brain microhemorrhages   |

| Species  | Route             | Dose           | Duration of Study | Results   |
|--|-------------------|----------------|-------------------|---|
|  | Bolus intrathecal | 100-1600 mcg** | 19 days           | agitation, pain, ↑ in heart rate and blood pressure, hindlimb dysfunction |
| <p>* Dosing was reduced to 1.0 mg / kg / day on day 5 due to severity of clinical signs<br/> ** Initial dose which was doubled daily up to 1600 mcg after which the maximum tolerated dose (800 mcg) was administered daily for 14 days.</p> |                   |                |                   |   |

The toxicological profile of remifentanil is consistent with that expected from a potent mc-opioid agonist. Clinical signs of opioid intoxication were observed in both rats and dogs. Respiratory depression led to death in some animals. The incidence of clonic convulsions increased with increasing days of dosing in both species in the 4-week bolus studies.

In the 4-week rat bolus study, slightly reduced absolute and relative epididymal weights were observed at 2.5 mg / kg / day and sloughed epithelial cells were noted in epididymal tubules at 0.25, 1.0 and 2.5 mg / kg / day. These observations are not predictive of effects in man, where clinical exposure is brief and at relatively low doses.

Continuous infusion of remifentanil to rats was associated with a reversible increase (up to 54%) in serum glucose. Microscopic findings were limited to a reversible decrease in pancreatic acinar cell zymogen granules in mid and high dose animals.

Microscopic brain hemorrhages were noted in the midbrain areas of dogs receiving 0.03 and 0.05 mg / kg (at least 15 times the maximum recommended human bolus dose of 2 mcg / kg). These hemorrhages were reversible and are thought to be due to hypoxia. Additional studies in ventilated dogs showed that adequate ventilation eliminated the occurrence of microhemorrhages or reduced their incidence to below that seen in dogs treated with saline alone.

Single and repeat dose comparator studies in non-ventilated dogs with bolus intravenous injections of up to 1 mg / kg alfentanil, resulted in morphologically identical microscopic brain hemorrhages, confirming that this finding was not specific to remifentanil.

Intrathecal administration of remifentanil to dogs produced hindlimb dysfunction and increased agitation and pain. Bolus intrathecal doses of the glycine formulation (without remifentanil) resulted in clinical observations of agitation and pain, but no microscopic evidence of tissue damage. These effects are believed to be secondary to the glycine excipient. Because of the better buffering properties of blood, the more rapid dilution, and the low glycine concentration of the Remifentanil Hydrochloride for Injection formulation, this finding has no clinical relevance for intravenous administration of Remifentanil Hydrochloride for Injection.

### **Reproduction and Teratology**

There were no adverse effects on the mating performance of male and female rats, as well as on fertility of female rats. The male fertility index (number of pregnancies / number of rats that mated) was reduced, probably due to decreases in testes and epididymal weights and increased incidences of macroscopic lesions and microscopic changes in these organs. However, these changes were observed only after prolonged exposure to relatively high doses of remifentanil and are not relevant to its clinical use.



In organogenesis studies in rats and rabbits, remifentanil was not considered to present a developmental hazard to fetuses. Maternal toxicity was considered responsible for the reduced fetal bodyweights in rats, as well as two abortions, increased incidences of resorption, and the increased fetal incidence of the skeletal variation of “greater than 12 full pair of ribs” in rabbits.

Placental and milk transfer studies showed that pups are exposed to remifentanil and / or its metabolites during growth and development.

### **Carcinogenesis and Mutagenesis**

Remifentanil, with or without a rat liver enzyme fraction (S9), was not mutagenic in the 5 strains of *Salmonella typhimurium* tested by gene mutation assay (Ames test) and did not produce chromosome aberrations in the Chinese hamster ovary cells. Remifentanil was also negative in the *in vivo* micronucleus test and the liver unscheduled DNA synthesis assay.

Remifentanil was found to be genotoxic in mammalian cells *in vitro* in the mouse lymphoma assay. Remifentanil concentrations over 4000 times greater than those seen with clinical use (50 ng / mL) were mutagenic only in the presence of metabolic activation.

## REFERENCES

These references are intended to support only approved indications in the product monograph and not the non-approved indications even though they may be mentioned in some of the publications listed.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**REMIFENTANIL HYDROCHLORIDE FOR INJECTION**

1 mg / vial, 2 mg / vial, 5 mg / vial of remifentanil (as remifentanil hydrochloride)

Read this carefully before you start taking Remifentanil Hydrochloride for Injection and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Remifentanil Hydrochloride for Injection.

**Serious Warnings and Precautions**

- **Even if you take Remifentanil Hydrochloride for Injection as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Remifentanil Hydrochloride for Injection. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your Remifentanil Hydrochloride for Injection. They could die from taking it. If a person has not been prescribed Remifentanil Hydrochloride for Injection taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Remifentanil Hydrochloride for Injection while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

**Seek immediate medical help for your baby.**

- **Taking Remifentanil Hydrochloride for Injection with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

**What is Remifentanil Hydrochloride for Injection used for?**

Remifentanil Hydrochloride for Injection is a pain medication. It is given along with other drugs

used for anesthesia by your doctor. It may be given to you:

- before and / or during surgery;
- if you are undergoing painful medical procedures;

### **How does Remifentanil Hydrochloride for Injection work?**

Remifentanil Hydrochloride for Injection is a fast acting pain relief medication and belongs to a class of medicines known as opioids. It provides pain relief for a short period of time. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

### **What are the ingredients in Remifentanil Hydrochloride for Injection?**

Medicinal ingredients: Remifentanil hydrochloride

Non-medicinal ingredients: Glycine, hydrochloric acid

### **Remifentanil Hydrochloride for Injection comes in the following dosage forms:**

Lyophilized Powder for Injection, 1 mg / vial, 2 mg / vial, 5 mg / vial of remifentanil

### **Do not use Remifentanil Hydrochloride for Injection if:**

- your doctor did not prescribe it for you
- you are allergic to remifentanil hydrochloride or any of the other ingredients in Remifentanil Hydrochloride for Injection
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Remifentanil Hydrochloride for Injection. Talk about any health conditions or problems you may have, including if you:**

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease

- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant.

**Other warnings you should know about:**

**Opioid dependence and addiction:** There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

**Pregnancy, nursing, labour and delivery:**

Opioids can be transferred to your baby through breast milk, or while still in the womb. Remifentanil Hydrochloride for Injection can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Remifentanil Hydrochloride for Injection outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Remifentanil Hydrochloride for Injection, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Remifentanil Hydrochloride for Injection. This may help avoid serious harm to your unborn baby.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to Remifentanil Hydrochloride for Injection. Remifentanil Hydrochloride for Injection can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off Remifentanil Hydrochloride for Injection.

**Serotonin Syndrome:** Remifentanil Hydrochloride for Injection can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take Remifentanil Hydrochloride for Injection with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**Sexual Function / Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Remifentanil Hydrochloride for Injection:**

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Remifentanil Hydrochloride for Injection. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Remifentanil Hydrochloride for Injection
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Remifentanil Hydrochloride for Injection with MAO inhibitors (MAOI) or if you have taken MAOI's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

**How to take Remifentanil Hydrochloride for Injection:**

## **Remifentanil Hydrochloride for Injection is given via an injection.**

You should be given it:

- only in a hospital or clinic that has the proper monitoring and support equipment in place.
- by a healthcare professional that has been specifically trained in the use of intravenous anesthetics.

**Usual dose:** Your doctor will decide the best dose for you. It will depend on your age, weight, your health, medications you are currently taking and the type of surgery you are having.

### **Overdose:**

If you think you have taken too much Remifentanil Hydrochloride for Injection, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

### **What are possible side effects from using Remifentanil Hydrochloride for Injection ?**

These are not all the possible side effects you may feel when taking Remifentanil Hydrochloride for Injection. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- High or low blood pressure
- Excessive sweating
- feeling of intense happiness or excitement (euphoria)
- feeling agitated
- crying
- headache



- trouble with your vision
- sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
- pain at the injection site
- feeling tired
- chills
- low sex drive, impotence (erectile dysfunction), infertility

| <b>Serious side effects and what to do about them</b>   |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| <b>COMMON</b><br>Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing  |                                      | x            |   |
| Drowsiness, dizziness.  |                                      | x            |   |
| Fast, slow, or uneven heartbeat.  |                                      | x            |   |
| Severe nausea or vomiting.  |                                      | x            |   |
| Stiffness in the muscles of your neck, chest, hands, or legs.   |                                      | x            |   |
| Trouble breathing, or chest tightness.  |                                      | x            |   |
| <b>UNCOMMON</b><br>Mild skin rash or itching.   | x                                    |              |   |
| Twitching or muscle movements you cannot control.   | x                                    |              |   |
| Pain, itching, burning, swelling, or lump under your skin where the needle is placed.   | x                                    |              |   |
| Twitching or muscle movements you cannot control.   | x                                    |              |   |
| <b>RARE</b><br>Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles / low muscle tone<br>cold and clammy skin. |                                      |              | x   |
| Respiratory Depression:<br>Slow, shallow or weak breathing.   |                                      |              | x   |
| Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or  |                                      |              | x   |

| <b>Serious side effects and what to do about them</b>   |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| breathing   |                                      |              |   |
| Bowel Blockage (impaction): abdominal pain, severe constipation, nausea   |                                      |              | x   |
| Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating. |                                      | x            |   |
| Fast, Slow or Irregular Heartbeat: heart palpitations.  |                                      | x            |   |
| Low Blood Pressure: dizziness, fainting, light-headedness.  | x                                    |              |   |
| Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea               |                                      |              | x   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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| <p><b>Reporting Side Effects</b></p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> <li>• Visiting the Web page on Adverse Reaction Reporting (<a href="https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html">https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html</a>) for information on how to report online, by mail or by fax; or</li> <li>• Calling toll-free at 1-866-234-2345.</li> </ul> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p> |
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**Storage:**

Remifentanil Hydrochloride for Injection should be stored at room temperature (15°C to 30°C).

**If you want more information about Remifentanil Hydrochloride for Injection:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and

includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.sterimaxinc.com](http://www.sterimaxinc.com), or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

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