Core Safety Profile

Active substance: Remifentanil
Pharmaceutical form(s)/strength: Powder for injection
P-RMS: DE/H/PSUR/0010/001
Date of FAR: 06.08.2009
4.2 Posology and Method of Administration

/.../shall be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

Continuous infusions of /.../must be administered by a calibrated infusion device into a fast flowing IV line or via a dedicated IV line. This infusion line should be connected at, or close to, the venous cannula and primed, to minimise the potential dead space (see section 6.6 for additional information, including tables with examples of infusion rates by body weight to help titrate /.../to the patient’s anaesthetic needs).

/.../may also be given by target-controlled infusion (TCI) with an approved infusion device incorporating the Minto pharmacokinetic model with covariates for age and lean body mass (LBM) (Anesthesiology 1997; 86: 10-23).

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual /.../after use (see section 4.4).

/.../is for intravenous use only and must not be administered by epidural or intrathecal injection (see section 4.3).

Dilution
/.../may be further diluted after reconstitution (see section 6.3 and 6.6 for storage conditions of the reconstituted/diluted product and the recommended diluents).

For manually-controlled infusion /.../can be diluted to concentrations of 20 to 250 μg/ml (50 μg/ml is the recommended dilution for adults and 20 to 25 μg/ml for paediatric patients aged 1 year and over).

For TCI the recommended dilution of /.../is 20 to 50 μg/ml.

4.2.1 General anaesthesia
The administration of /.../must be individualised based on the patient’s response.

4.2.1.1 Adults
Administration by Manually-Controlled Infusion
The following table summarises the starting injection/infusion rates and dose range:
Dosing Guidelines for Adults

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>BOLUS INJECTION (µg/kg)</th>
<th>CONTINUOUS INFUSION (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Starting Rate</td>
</tr>
<tr>
<td>Induction of anaesthesia</td>
<td>1 (give over not less than 30 seconds)</td>
<td>0.5 to 1</td>
</tr>
<tr>
<td>Maintenance of anaesthesia in ventilated patients</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>• Nitrous oxide (66%)</td>
<td>0.5 to 1</td>
<td>0.25</td>
</tr>
<tr>
<td>• Isoflurane (starting dose 0.5 MAC)</td>
<td>0.5 to 1</td>
<td>0.25</td>
</tr>
<tr>
<td>• Propofol (starting dose 100 µg/kg/min)</td>
<td>0.5 to 1</td>
<td>0.25</td>
</tr>
</tbody>
</table>

When given by slow bolus injection /.../shall be administered over not less than 30 seconds.

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see Concomitant medication).

No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with remifentanil.

**Induction of anaesthesia:** /.../should be administered with a standard dose of hypnotic agent, such as propofol, thiopental, or isoflurane, for the induction of anaesthesia. /.../can be administered at an infusion rate of 0.5 to 1 µg/kg/min, with or without an initial slow bolus injection of 1 µg/kg given over not less than 30 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the infusion of Ultiva, then a bolus injection is not necessary.

**Maintenance of anaesthesia in ventilated patients:** After endotracheal intubation, the infusion rate of /.../should be decreased, according to anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of Ultiva, the rate of administration during anaesthesia 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 µ-opioid response. In response to light anaesthesia, supplemental slow bolus injections may be administered every 2 to 5 minutes.

**Anaesthesia in spontaneously breathing anaesthetised patients with a secured airway (e.g. laryngeal mask anaesthesia):** In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. The recommended starting infusion rate for supplemental analgesia in spontaneously breathing anaesthetised patients is 0.04 µg/kg/min with titration to effect. A range of infusion rates from 0.025 to 0.1 µg/kg/min has been studied.
Bolus injections are not recommended in spontaneously breathing anaesthetised patients. 

...should not be used as an analgesic in procedures where patients remain conscious or do not receive any airway support during the procedure.

**Concomitant medication:** Remifentanil decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).

Doses of the following agents used in anaesthesia: isoflurane, thiopentone, propofol and temazepam have been reduced by up to 75% when used concurrently with remifentanil.

**Guidelines for discontinuation/continuation into the immediate post-operative period:** Due to the very rapid offset of action of.../no residual opioid activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Ultiva. 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 post-operative care.

In the event that longer acting analgesia has not been established prior to the end of surgery, .../may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.

Guidance on use in mechanically ventilated intensive care patients is provided in section 4.2.3.

In patients who are breathing spontaneously, the infusion rate of .../should initially be decreased to a rate of 0.1 μg/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025 μg/kg/min every five minutes, to balance the patient’s level of analgesia and respiratory rate. .../should only be used in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, under the close supervision of persons specifically trained in the recognition and management of the respiratory effects of potent opioids.

The use of bolus injections of .../to treat pain during the post-operative period is not recommended in patients who are breathing spontaneously.

**Administration by Target-Controlled Infusion**

**Induction and maintenance of anaesthesia in ventilated patients:** .../TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table in section 4.2.1.1.). In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanil concentrations ranging from 3 to 8 ng/ml. .../should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 ng/ml may be required.

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see Table and Concomitant medication subsection in 4.2.1.1).

For information on blood remifentanil concentrations achieved with manually-controlled infusion see Table 6.
As there are insufficient data, the administration of /.../by TCI for spontaneous ventilation anaesthesia is not recommended.

**Guidelines for discontinuation/continuation into the immediate post-operative period:**

At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see Guidelines for discontinuation under Administration by manually-controlled infusion in section 4.2.1.1.).

As there are insufficient data, the administration of /.../by TCI for the management of post-operative analgesia is not recommended.

**4.2.1.2 Paediatric patients (1 to 12 years of age)**

Co-administration of /.../with induction agents has not been studied. /.../TCI has not been studied in paediatric patients and therefore administration of /.../by TCI is not recommended in these patients. The following doses of /.../are recommended for maintenance of anaesthesia:

**Dosing Guidelines for Paediatric Patients (1 to 12 years of age)**

<table>
<thead>
<tr>
<th><em>CONCOMITANT ANAESTHETIC AGENT</em></th>
<th><strong>BOLUS INJECTION (µg/kg)</strong></th>
<th><strong>CONTINUOUS INFUSION (µg/kg/min)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting Rate</td>
<td>Typical Maintenance Rates</td>
</tr>
<tr>
<td>Halothane (starting dose 0.3 MAC)</td>
<td>1</td>
<td>0.25 0.05 to 1.3</td>
</tr>
<tr>
<td>Sevoflurane (starting dose 0.3 MAC)</td>
<td>1</td>
<td>0.25 0.05 to 0.9</td>
</tr>
<tr>
<td>Isoflurane (starting dose 0.5 MAC)</td>
<td>1</td>
<td>0.25 0.06 to 0.9</td>
</tr>
</tbody>
</table>

*co-administered with nitrous oxide/oxygen in a ratio of 2:1

When given by bolus injection, /.../should be administered over not less than 30 seconds. Surgery should not commence until at least 5 minutes after the start of the /.../infusion, if a simultaneous bolus dose has not been given. For sole administration of nitrous oxide (70%) with Ultiva, typical maintenance infusion rates should be between 0.4 and 3 µg/kg/min, and although not specifically studied, adult data suggest that 0.4 µg/kg/min is an appropriate starting rate. Paediatric patients should be monitored and the dose titrated to the depth of analgesia appropriate for the surgical procedure.

**Concomitant medication:** At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane, halothane and sevoflurane should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia. No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with remifentanil (see section 4.2.1.1. Adults - concomitant medication).
Guidelines for patient management in the immediate post-operative period

Establishment of alternative analgesia prior to discontinuation of Ultiva: Due to the very rapid offset of action of Ultiva, no residual activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Ultiva. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient’s surgical procedure and the level of post-operative care anticipated (see section 4.4.).

4.2.1.3 Neonates/infants (aged less than 1 year)
The pharmacokinetic profile of remifentanil in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction for body weight differences. However, because there are insufficient clinical data, the administration of /.../is not recommended for this age group.

4.2.2 Cardiac anaesthesia
Administration by Manually-Controlled Infusion

Dosing Guidelines for Cardiac Anaesthesia

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>BOULUS INJECTION ($\mu g$/kg)</th>
<th>CONTINUOUS INFUSION ($\mu g$/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Starting Rate</td>
</tr>
<tr>
<td>Intubation</td>
<td>Not recommended</td>
<td>1</td>
</tr>
<tr>
<td>Maintenance of anaesthesia</td>
<td></td>
<td>0.5 to 1</td>
</tr>
<tr>
<td>• Isoflurane (starting dose 0.4 MAC)</td>
<td></td>
<td>0.5 to 1</td>
</tr>
<tr>
<td>• Propofol (starting dose 50 $\mu g$/kg/min)</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Continuation of post-operative analgesia, prior to extubation</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Induction period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, /.../should be administered at an initial infusion rate of 1 $\mu g$/kg/min. The use of bolus injections of /.../during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 5 minutes after the start of the infusion.

Maintenance period of anaesthesia: After endotracheal intubation the infusion rate of /.../should be titrated according to patient need. Supplemental slow bolus doses may also be given as required. High-risk cardiac patients, such as those with poor ventricular function or undergoing valve surgery, should be administered a maximum bolus dose of 0.5 $\mu g$/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see section 5.2 Pharmacokinetic properties - cardiac anaesthesia).
Concomitant medication: At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia. No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with remifentanil (see section 4.2.1.1. Adults - concomitant medication).

Guidelines for post-operative patient management

Continuation of /.../post-operatively to provide analgesia prior to weaning for extubation: It is recommended that the infusion of /.../should be maintained at the final intra-operative rate during transfer of patients to the post-operative care area. Upon arrival into this area, the patient’s level of analgesia and sedation should be closely monitored and the /.../infusion rate adjusted to meet the individual patient’s requirements (see section 4.2.3 for further information on management of intensive care patients).

Establishment of alternative analgesia prior to discontinuation of Ultiva: Due to the very rapid offset of action of Ultiva, no residual opioid activity will be present within 5 to 10 minutes after discontinuation. Prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents at a sufficient time in advance to allow the therapeutic effects of these agents to become established. It is therefore recommended that the choice of agent(s), the dose and the time of administration are planned, before weaning the patient from the ventilator.

Guidelines for discontinuation of Ultiva: Due to the very rapid offset of action of Ultiva, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of /.../(see section 4.8). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the /.../infusion is discontinued. The infusion rate should be reduced by 25% decrements in at least 10 minute intervals until the infusion is discontinued.

During weaning from the ventilator the /.../infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics. Haemodynamic changes such as hypertension and tachycardia should be treated with alternative agents as appropriate.

When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

Administration by Target-Controlled Infusion

Induction and maintenance of anaesthesia: /.../TCI should be used in association with an intravenous or inhalational hypnotic agent during the induction and maintenance of anaesthesia in ventilated adult patients (see Table in section 4.2.2.). In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 ng/ml have been used in clinical studies. At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see Table and Concomitant medication subsection in 4.2.2).
For information on blood remifentanil concentrations achieved with manually-controlled infusion see Table 6.

**Guidelines for discontinuation/continuation into the immediate post-operative period:**
At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see Guidelines for discontinuation under Administration by manually-controlled infusion in section 4.2.2.). As there are insufficient data, the administration of /.../by TCI for the management of post-operative analgesia is not recommended.

**4.2.3  Use in intensive care**
/.../can be used for the provision of analgesia in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.

The safety and efficacy from well-controlled clinical trials of /.../in mechanically ventilated intensive care patients has been established for durations up to 3 days (see section 4.2.3.2. and section 5.2). Therefore, the use of /.../is not recommended for a duration of treatment greater than 3 days.

/.../TCI has not been studied in intensive care patients and therefore administration of /.../by TCI is not recommended in these patients.

In adults, it is recommended that /.../is initiated at an infusion rate of 0.1 µg/kg/min (6 µg/kg/h) to 0.15 µg/kg/min (9 µg/kg/h). The infusion rate should be titrated in increments of 0.025 µg/kg/min (1.5 µg/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The patient should be regularly assessed and the /.../infusion rate adjusted accordingly. If an infusion rate of 0.2 µg/kg/min (12 µg/kg/h) is reached and sedation is required, it is recommended that dosing with an appropriate sedative agent is initiated (see below). The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the /.../infusion rate in increments of 0.025 µg/kg/min (1.5 µg/kg/h) may be made if additional analgesia is required.

The following table summarises the starting infusion rates and typical dose range for provision of analgesia in individual patients:

**Dosing Guidelines for use of /.../within the Intensive Care Setting**

<table>
<thead>
<tr>
<th>CONTINUOUS INFUSION µg/kg/min (µg/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Rate</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>0.1(6) to 0.15 (9)</td>
</tr>
</tbody>
</table>

Bolus doses of /.../are not recommended in the intensive care setting.

The use of /.../will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given below.
<table>
<thead>
<tr>
<th>Sedative Agents</th>
<th>Bolus (mg/kg)</th>
<th>Infusion (mg/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>Up to 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Up to 0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

To allow separate titration of the respective agents, sedative agents should not be administered as an admixture.

**Additional analgesia for ventilated patients undergoing stimulating procedures:** An increase in the existing infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that an infusion rate of at least 0.1 µg/kg/min (6 µg/kg/h) should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 µg/kg/min (15 µg/kg/h), maximum 0.74 µg/kg/min (45 µg/kg/h), has been administered for provision of additional anaesthesia during stimulating procedures.

**Establishment of alternative analgesia prior to discontinuation of Ultiva:** Due to the very rapid offset of action of Ultiva, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Following administration of Ultiva, the possibility of tolerance and hyperalgesia should be considered. Therefore, prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents to prevent hyperalgesia and associated haemodynamic changes. These agents must be given at a sufficient time in advance to allow the therapeutic effects of these agents to become established. The range of options for analgesia includes long acting oral, intravenous, or regional analgesics controlled by the nurse or the patient. These techniques should always be titrated to individual patient needs as the infusion of Ultiva is reduced. It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to discontinuation of Ultiva.

There is a potential for the development of tolerance with time during prolonged administration of μ-opioid agonists.

**Guidelines for extubation and discontinuation of Ultiva:** In order to ensure a smooth emergence from an Ultiva-based regimen it is recommended that the infusion rate is titrated in stages to 0.1 µg/kg/min (6 µg/kg/h) over a period up to 1 hour prior to extubation.

Following extubation, the infusion rate should be reduced by 25% decrements in at least 10-minute intervals until the infusion is discontinued. During weaning from the ventilator the infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of Ultiva, the IV cannula should be cleared or removed to prevent subsequent inadvertent administration.

**When other opioid agents are administered as part of the regimen for transition to alternative analgesia,** the patient must be carefully monitored. The benefit of providing adequate analgesia must always be balanced against the potential risk of respiratory depression with these agents.
4.2.3.1 Paediatric intensive care patients
There are no data available on use in paediatric patients.

4.2.3.2 Renally-impaired intensive care patients
No adjustments to the doses recommended above are necessary in renally-impaired patients including those undergoing renal replacement therapy, however the clearance of the carboxylic acid metabolite is reduced in patients with renal impairment (see section 5.2).

4.2.4 Special patient populations

4.2.4.1 Elderly (over 65 years of age)
**General anaesthesia:** The initial starting dose of remifentanil administered to patients over 65 should be half the recommended adult dose and then shall be titrated to individual patient need as an increased sensitivity to the pharmacological effects of remifentanil has been seen in this patient population. This dose adjustment applies to use in all phases of anaesthesia including induction, maintenance, and immediate post-operative analgesia. Because of the increased sensitivity of elderly patients to Ultiva, when administering /.../by TCI in this population the initial target concentration should be 1.5 to 4 ng/ml with subsequent titration to response.

**Cardiac anaesthesia:** No initial dose reduction is required (see section 4.2.2.).

**Intensive Care:** No initial dose reduction is required (see section 4.2.3.).

4.2.4.2 Obese patients
For manually-controlled infusion it is recommended that for obese patients the dosage of /.../should be reduced and based upon ideal body weight as the clearance and volume of distribution of remifentanil are better correlated with ideal body weight than actual body weight.

With the calculation of lean body mass (LBM) used in the Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m² and in male patients with BMI greater than 40 kg/m². To avoid underdosing in these patients, remifentanil TCI should be titrated carefully to individual response.

4.2.4.3 Renal impairment
On the basis of investigations carried out to date, a dose adjustment in patients with impaired renal function, including intensive care patients, is not necessary.

4.2.4.4 Hepatic impairment
Studies carried out with a limited number of patients with impaired liver function, do not justify any special dosage recommendations. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil (see section 4.4). These patients shall be closely monitored and the dose of remifentanil shall be titrated to individual patient need.

4.2.4.5 Neurosurgery
Limited clinical experience in patients undergoing neurosurgery has shown that no special dosage recommendations are required.

4.2.4.6 ASA III/IV patients
**General anaesthesia:** As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised in the administration of /.../in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended. In paediatric patients, there are insufficient data to make a dosage recommendation.
For TCI, a lower initial target of 1.5 to 4 ng/ml should be used in ASA III or IV patients and subsequently titrated to response.

**Cardiac anaesthesia:** No initial dose reduction is required (see section 4.2.2.).

### 4.3 Contra-indications

As glycine is present in the formulation, /.../is contra-indicated for epidural and intrathecal use (see Preclinical safety data).

/.../is contra-indicated in patients with hypersensitivity to the active substance or other fentanyl analogues or to any of the excipients.

/.../is contra-indicated for use as the sole agent for induction of anaesthesia.

### 4.4 Special Warnings and Precautions for Use

/.../shall be administered only in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, and by persons specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation. Such training must include the establishment and maintenance of a patent airway and assisted ventilation. The use of /.../in mechanically ventilated intensive care patients is not recommended for a duration of treatment greater than 3 days.

#### Rapid offset of action/Transition to alternative analgesia

Due to the very rapid offset of action of Ultiva, no residual opioid activity will be present within 5 to 10 minutes after the discontinuation of Ultiva. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Ultiva. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit. Prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents. Sufficient time must be allowed to reach the therapeutic effect of the longer acting analgesic. The choice of agent(s), the dose and the time of administration should be planned in advance and individually tailored to be appropriate for the patient’s surgical procedure and the level of post-operative care anticipated. When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

#### Discontinuation of treatment

Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of /.../in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

#### Muscle rigidity - prevention and management

At the doses recommended muscle rigidity may occur. As with other opioids, the incidence of muscle rigidity is related to the dose and rate of administration. Therefore, slow bolus injections shall be administered over not less than 30 seconds.
Muscle rigidity induced by remifentanil must be treated in the context of the patient's clinical condition with appropriate supporting measures. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of remifentanil as an analgesic may be treated by stopping or decreasing the rate of administration of remifentanil. Resolution of muscle rigidity after discontinuing the infusion of remifentanil occurs within minutes. Alternatively, an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of remifentanil.

**Respiratory depression - prevention and management**  
As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, remifentanil shall only be used in areas where facilities for monitoring and dealing with respiratory depression are available. Special care should be taken in patients with respiratory dysfunction. The appearance of respiratory depression shall be managed appropriately, including decreasing the rate of infusion by 50%, or a temporary discontinuation of the infusion. Unlike other fentanyl analogues, remifentanil has not been shown to cause recurrent respiratory depression, even after prolonged administration. However, as many factors may affect post-operative recovery it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

**Cardiovascular effects**  
The risk of cardiovascular effects such as hypotension and bradycardia, which may rarely lead to asystole/cardiac arrest (see section 4.5 and 4.8) may be reduced by lowering the rate of infusion of /.../ or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate.

Debilitated, hypovolaemic, hypotensive and elderly patients may be more sensitive to the cardiovascular effects of remifentanil.

**Inadvertent administration**  
A sufficient amount of /.../ may be present in the dead space of the IV line and/or cannula to cause respiratory depression, apnoea and/or muscle rigidity if the line is flushed with IV fluids or other drugs. This may be avoided by administering /.../ into a fast flowing IV line or via a dedicated IV line, which is removed when /.../ is discontinued.

**Neonates/infants**  
There are no data available on use in neonates/infants under 1 year of age.

**Drug abuse**  
As with other opioids remifentanil may produce dependency.

4.5 **Interaction with Other Medicinal Products and Other Forms of Interaction**  
Remifentanil is not metabolised by plasmacholinesterase, therefore, interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, remifentanil, whether given by manually-controlled infusion or TCI, decreases the doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see section 4.2). If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.
The cardiovascular effects of hypotension and bradycardia – see section 4.4 and 4.8), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents.

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether remifentanil is excreted in human milk. However, because fentanyl analogues are excreted in human milk and remifentanil-related material was found in rat milk after dosing with remifentanil, nursing mothers should be advised to discontinue breast feeding for 24 hours following administration of remifentanil.

Labour and delivery

There are insufficient data to recommend remifentanil for use during labour and caesarean section. It is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

4.7 Effects on Ability to Drive and use Machines

After anaesthesia with remifentanil the patient should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

4.8 Undesirable Effects

The most common undesirable effects associated with remifentanil are direct extensions of μ-opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil administration. The frequencies below are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune System Disorders

Rare: Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents.

Psychiatric disorders

Not known: Drug dependence

Nervous System Disorders

Very common: Skeletal muscle rigidity
Rare: Sedation (during recovery from general anaesthesia)

Not known: Convulsions
Cardiac Disorders
Common: Bradycardia
Rare: Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents.
Not known: Atrioventricular block

Vascular Disorders
Very common: Hypotension
Common: Post-operative hypertension

Respiratory, Thoracic and Mediastinal Disorders
Common: Acute respiratory depression, apnoea
Uncommon: Hypoxia

Gastrointestinal Disorders
Very common: Nausea, vomiting
Uncommon: Constipation

Skin and Subcutaneous Tissue Disorders
Common: Pruritus

General Disorders and Administration Site Conditions
Common: Post-operative shivering
Uncommon: Post-operative aches
Not known: Drug tolerance

Discontinuation of treatment
Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days (see section 4.4).

4.9 Overdose
As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil. Due to the very short duration of action of Ultiva, the potential for deleterious effects due to overdose are limited to the immediate time period following drug administration. Response to discontinuation of the drug is rapid, with return to baseline within ten minutes.

In the event of overdose or suspected overdose, take the following actions: discontinue administration of Ultiva, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function. If depressed respiration is associated with muscle rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor for the treatment of hypotension and other supportive measures may be employed.

Intravenous administration of an opioid antagonist such as naloxone may be given as a specific antidote to manage severe respiratory depression and muscle rigidity. The duration of respiratory depression following overdose with /.../is unlikely to exceed the duration of action of the opioid antagonist.