

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Remifentanyl 2 mg, powder for concentrate for solution for injection or infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 2 mg remifentanyl (as hydrochloride).

After reconstitution the solution contains 1 mg/ml of remifentanyl (as hydrochloride), if prepared as recommended (see section 6.6).

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for concentrate for solution for injection or infusion.

White to off white powder.

pH of the reconstituted solution: 2.5 to 3.5.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Remifentanyl is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia. Remifentanyl is indicated for provision of analgesia in mechanically ventilated intensive care patients 18 years of age and over.

### 4.2 Posology and method of administration

**Remifentanyl 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 Remifentanyl must be administered by a calibrated infusion device into a fast flowing IV line or via a dedicated I.V. 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).

Remifentanyl 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 Remifentanyl after use (see section 4.4).

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

### Dilution

Remifentanyl may be further diluted after reconstitution (see sections 6.3 and 6.6).

For manually-controlled infusion Remifentanyl 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 Remifentanyl is 20 to 50 µg/ml.

**General anaesthesia**

The administration of Remifentanyl must be individualised based on the patient’s response.

**Adults**

**Administration by Manually-Controlled Infusion**

The following table summarises the starting injection/infusion rates and dose range:

**Dosing Guidelines for Adults**

INDICATION	BOLUS INJECTION (µg/kg)	CONTINUOUS INFUSION (µg/kg/min)	
		Starting Rate	Range
Induction of anaesthesia	1 (give over not less than 30 seconds)	0.5 to 1	–
maintenance of anaesthesia in ventilated patients <ul style="list-style-type: none"><li>Nitrous oxide (66%)</li><li>Isoflurane</li><li>(starting dose 0.5 MAC)</li><li>Propofol</li><li>(starting dose 100 µg/kg/min)</li></ul>	0.5 to 1	0.4	0.1 to 2
	0.5 to 1	0.25	0.05 to 2
	0.5 to 1	0.25	0.05 to 2

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

At the doses recommended above, remifentanyl 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 remifentanyl.

**Induction of anaesthesia:**

Remifentanyl should be administered with a standard dose of hypnotic agent, such as propofol, thiopental, or isoflurane, for the induction of anaesthesia.

Administering Remifentanyl after a hypnotic agent will reduce the incidence of muscle rigidity.

Remifentanyl 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 Remifentanyl, then a bolus injection is not necessary.

**Maintenance of anaesthesia in ventilated patients:**

After endotracheal intubation, the infusion rate of Remifentanyl should be decreased, according to anaesthetic technique, as indicated in the above table.

Due to the fast onset and short duration of action of Remifentanyl, 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. There is also a risk that muscle rigidity may occur. Therefore attention must be given to respiratory effects eventually combined with muscular rigidity. Special care is needed to adjust the dose to the patient requirements and ventilatory support and/or urgent intubation may be required. Adequate facilities should be available for monitoring of patients administered Remifentanyl. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression including intubation and/or muscle rigidity (see section 4.4).

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.

Remifentanyl 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:**

Remifentanyl 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 remifentanyl.

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

Due to the very rapid offset of action of Remifentanyl 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 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 post-operative care.

In the event that longer acting analgesia has not been established prior to the end of surgery, Remifentanyl 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 Use in intensive care.

In patients who are breathing spontaneously, the infusion rate of Remifentanyl 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.

Remifentanyl 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 Remifentanyl 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:**

Remifentanyl 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 Adults).

In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanyl concentrations ranging from 3 to 8 ng/ml.

Remifentanyl 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 Adults).

For information on blood remifentanil concentrations achieved with manually-controlled infusion see Table 6.

As there are insufficient data, the administration of Remifentanil 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 Adults.).

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

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

Co-administration of Remifentanil and an intravenous anaesthetic agent for induction of anaesthesia has not been studied in detail and is therefore not recommended.

Remifentanil TCI has not been studied in paediatric patients and therefore administration of Remifentanil by TCI is not recommended in these patients.

The following doses of Remifentanil are recommended for maintenance of anaesthesia:

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

*CONCOMITANT ANAESTHETIC AGENT	BOLUS INJECTION (µg/kg)	CONTINUOUS INFUSION (µg /kg/min)	
		Starting Rate	Typical maintenance Rates
Halothane (starting dose 0.3 MAC)	1	0.25	0.05 to 1.3
Sevoflurane (starting dose 0.3 MAC)	1	0.25	0.05 to 0.9
Isoflurane (starting dose 0.5 MAC)	1	0.25	0.06 to 0.9

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

When given by bolus injection, Remifentanil should be administered **over not less than 30 seconds**.

Surgery should not commence until at least 5 minutes after the start of the Remifentanil infusion, if a simultaneous bolus dose has not been given. For sole administration of nitrous oxide (70%) with Remifentanil, 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, remifentanyl 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 remifentanyl (see section Adults - concomitant medication).

**Guidelines for patient management in the immediate post-operative period**

**Establishment of alternative analgesia prior to discontinuation of Remifentanyl:**

Due to the very rapid offset of action of Remifentanyl, 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 Remifentanyl. 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).

**Neonates/infants (aged less than 1 year)**

There is limited clinical trial experience of remifentanyl in neonates and infants (aged under 1 year old; see section 5.1). The pharmacokinetic profile of remifentanyl in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction for body weight differences. (see section 5.2.). However, because there are insufficient clinical data, the administration of Remifentanyl is not recommended for this age group.  
Use for Total Intravenous anaesthesia (TIVA): There is limited clinical trial experience of remifentanyl for TIVA in infants (see section 5.1). However, there are insufficient clinical data to make dosage recommendations.

**Cardiac anaesthesia**

**Administration by Manually-Controlled Infusion**

**Dosing Guidelines for Cardiac Anaesthesia**

INDICATION	BOLUS INJECTION (µg/kg)	CONTINUOUS INFUSION (µg/kg/min)	
		Starting Rate	Typical Infusion Rates
Induction	Not recommended	1	–
Maintenance of anaesthesia			
• Isoflurane (starting dose 0.4 MAC)	0.5 to 1	1	0.003 to 4
• Propofol (starting dose 50 µg/kg/min)	0.5 to 1	1	0.01 to 4.3
Continuation of post-operative analgesia, prior to extubation	Not recommended	1	0 to 1

There are no sufficient data available on use in patients under 18 years of age undergoing cardiac surgery to establish dose recommendations for this population.

Remifentanyl is not recommended for use in patients with poor left ventricular function (left ventricular ejection fraction less than 0.35), since the safe use of the product in this patient group has not been established.

**Induction period of anaesthesia:**

After administration of hypnotic to achieve loss of consciousness, Remifentanyl should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus injections of Remifentanyl 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 Remifentanyl 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 µg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see section 5.2).

**Concomitant medication:**

At the doses recommended above, remifentanyl 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 remifentanyl (see section Adults - concomitant medication).

**Guidelines for post-operative patient management****Continuation of Remifentanyl post-operatively to provide analgesia prior to weaning for extubation:**

It is recommended that the infusion of Remifentanyl 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 Remifentanyl infusion rate adjusted to meet the individual patient's requirements (see section Use in intensive care for further information on management of intensive care patients).

**Establishment of alternative analgesia prior to discontinuation of Remifentanyl:**

Due to the very rapid offset of action of Remifentanyl, no residual opioid activity will be present within 5 to 10 minutes after discontinuation. Prior to discontinuation of Remifentanyl, 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 Remifentanyl:**

Due to the very rapid offset of action of Remifentanyl, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of Remifentanyl (see section 4.8). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the Remifentanyl 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 Remifentanyl 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:**

Remifentanyl 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 Cardiac anaesthesia).

In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanyl concentrations used for general surgical procedures. Following titration of remifentanyl to individual patient response, blood concentrations as high as 20 ng/ml have been used in clinical studies.

At the doses recommended above, remifentanyl 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 Cardiac anaesthesia).

For information on blood remifentanyl 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 remifentanyl 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 Cardiac anaesthesia).

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

**Use in intensive care**

Remifentanyl can be used for the provision of analgesia in mechanically ventilated intensive care patients of 18 years of age and over. Sedative agents should be added as appropriate.

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

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

In adults, it is recommended that Remifentanyl 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 Remifentanyl 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 Remifentanyl 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 Remifentanyl within the Intensive Care Setting**

CONTINUOUS INFUSION	
µg/kg/min (µg/kg/h)	
Starting Rate	Range
0.1(6) to 0.15 (9)	0.006 (0.36) to 0.74 (44.4)

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

The use of Remifentanyl will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given below.

**Recommended starting dose of sedative agents, if required:**

Sedative Agents	Bolus (mg/kg)	Infusion (mg/kg/h)
Propofol	Up to 0.5	0.5
Midazolam	Up to 0.03	0.03

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 Remifentanyl 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 a Remifentanyl 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 Remifentanyl**

Due to the very rapid offset of action of Remifentanyl no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion.

Following administration of Remifentanyl the possibility of tolerance and hyperalgesia should be considered. Therefore, prior to discontinuation of Remifentanyl 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 Remifentanyl is reduced. It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to discontinuation of Remifentanyl.

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

**Guidelines for extubation and discontinuation of Remifentanyl**

In order to ensure a smooth emergence from a Remifentanyl based regimen it is recommended that the infusion rate of Remifentanyl 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 Remifentanyl infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of Remifentanyl 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.**

**Paediatric intensive care patients**

The use of remifentanyl in intensive care patients under the age of 18 years is not recommended as there are no data available in this patient population.



**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).

**Special patient populations****Elderly (over 65 years of age)****General anaesthesia:**

The initial starting dose of remifentanyl 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 remifentanyl 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 Remifentanyl when administering Remifentanyl 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 Cardiac anaesthesia).

**Intensive Care:**

No initial dose reduction is required (see section Use in intensive care).

**Obese patients**

For manually-controlled infusion it is recommended that for obese patients the dosage of Remifentanyl should be reduced and based upon ideal body weight as the clearance and volume of distribution of remifentanyl 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/m<sup>2</sup> and in male patients with BMI greater than 40 kg/m<sup>2</sup>. To avoid underdosing in these patients, remifentanyl TCI should be titrated carefully to individual response.

**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.

**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 remifentanyl (see section 4.4).

These patients shall be closely monitored and the dose of remifentanyl shall be titrated to individual patient need.

**Neurosurgery**

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

**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 Remifentanyl 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 Cardiac anaesthesia).

The following tables give guidelines for infusion rates of Remifentanil for manually-controlled infusion:

**Table 1. Remifentanil for Injection Infusion Rates (ml/kg/h)**

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of			
	20 µg/ml 1 mg/50 ml	25 µg/ml 1 mg/40 ml	50 µg/ml 1 mg/20 ml	250 µg/ml 10 mg/40 ml
0.0125	0.038	0.03	0.015	Not recommended
0.025	0.075	0.06	0.03	Not recommended
0.05	0.15	0.12	0.06	0.012
0.075	0.23	0.18	0.09	0.018
0.1	0.3	0.24	0.12	0.024
0.15	0.45	0.36	0.18	0.036
0.2	0.6	0.48	0.24	0.048
0.25	0.75	0.6	0.3	0.06
0.5	1.5	1.2	0.6	0.12
0.75	2.25	1.8	0.9	0.18
1.0	3.0	2.4	1.2	0.24
1.25	3.75	3.0	1.5	0.3
1.5	4.5	3.6	1.8	0.36
1.75	5.25	4.2	2.1	0.42
2.0	6.0	4.8	2.4	0.48

**Table 2. Remifentanil for Injection Infusion Rates (ml/h) for a 20 µg/ml Solution**

Infusion Rate (µg/kg/min)	Patient Weight (kg)						
	5	10	20	30	40	50	60
0.0125	0.188	0.375	0.75	1.125	1.5	1.875	2.25
0.025	0.375	0.75	1.5	2.25	3.0	3.75	4.5
0.05	0.75	1.5	3.0	4.5	6.0	7.5	9.0
0.075	1.125	2.25	4.5	6.75	9.0	11.25	13.5
0.1	1.5	3.0	6.0	9.0	12.0	15.0	18.0
0.15	2.25	4.5	9.0	13.5	18.0	22.5	27.0
0.2	3.0	6.0	12.0	18.0	24.0	30.0	36.0
0.25	3.75	7.5	15.0	22.5	30.0	37.5	45.0
0.3	4.5	9.0	18.0	27.0	36.0	45.0	54.0
0.35	5.25	10.5	21.0	31.5	42.0	52.5	63.0
0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

**Table 3. Remifentanil for Injection Infusion Rates (ml/h) for a 25 µg/ml Solution**

Infusion Rate (µg/kg/min)	Patient Weight (kg)									
	10	20	30	40	50	60	70	80	90	100
0.0125	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.025	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.05	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.075	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.1	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.15	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
0.2	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4	43.2	48.0

Table 4. Remifentanil for Injection Infusion Rates (ml/h) for a 50 µg/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)							
	30	40	50	60	70	80	90	100
0.025	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
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 5. Remifentanil for Injection Infusion Rates (ml/h) for a 250 µg/ml Solution

Infusion Rate (µg/kg/min)	Patient Weight (kg)							
	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

The following table provides the equivalent blood remifentanil concentration using a TCI approach for various manually-controlled infusion rates at steady state:

Table 6. Remifentanil Blood Concentrations (ng/ml) estimated using the Minto (1997) Pharmacokinetic Model in a 70 kg, 170 cm, 40 Year Old Male Patient for Various Manually-Controlled Infusion rates (µg/kg/min) at Steady State.

Remifentanil Infusion Rate (µg/kg/min)	Remifentanil Blood Concentration (ng/ml)
0.05	1.3
0.10	2.6
0.25	6.3
0.40	10.4
0.50	12.6
1.0	25.2
2.0	50.5

4.3 Contraindications

As glycine is present in the formulation, Remifentanil is contra-indicated for epidural and intrathecal use (see section 5.3).

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

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

#### **4.4 Special warnings and precautions for use**

**Remifentanyl 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 Remifentanyl 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 Remifentanyl, no residual opioid activity will be present within 5 to 10 minutes after the discontinuation of Remifentanyl.

For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Remifentanyl.

The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit.

Prior to discontinuation of Remifentanyl, 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**

Common post-operative events associated with the emergence from general anaesthesia, such as shivering, agitation, tachycardia, hypertension, may occur earlier following discontinuation of Remifentanyl.

Symptoms following withdrawal of remifentanyl 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 Remifentanyl 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, sometimes severe, 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 remifentanyl must be treated in the context of the patients 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 remifentanyl as an analgesic may be treated by stopping or decreasing the rate of administration of remifentanyl. Resolution of muscle rigidity after discontinuing the infusion of remifentanyl occurs within minutes.

Alternatively an opioid antagonist may be administered, however this may reverse or attenuate the analgesic effect of remifentanyl.

### **Respiratory depression - prevention and management**

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. There are reports of patients with delayed respiratory depression 20-30 minutes after the remifentanyl infusion has been discontinued. Therefore, remifentanyl 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, remifentanyl 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 sections 4.5 and 4.8) may be reduced by lowering the rate of infusion of Remifentanyl 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 remifentanyl.

### **Inadvertent administration**

A sufficient amount of Remifentanyl 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 Remifentanyl into a fast flowing IV line or via a dedicated IV line, which is removed when Remifentanyl is discontinued.

### **Neonates/infants**

There is limited data available on use in neonates/infants under 1 year of age (see sections 4.2 – Neonates/infants (aged less than 1 year) and 5.1).

### **Drug abuse**

As with other opioids remifentanyl may produce dependency.

### **Athletes**

This medicine contains an active substance that may give a positive result in anti-doping tests.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Remifentanyl is not metabolised by plasmacholinesterase, therefore, interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, remifentanyl, 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.

Information of drug interactions with other opioids in relation to anaesthesia is very limited.

The cardiovascular effects of Remifentanyl (hypotension and bradycardia – see sections 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 Fertility, pregnancy and lactation**

There are no adequate and well-controlled studies in pregnant women.

In a human clinical trial, the concentration of remifentanyl in foetal blood was approximately 50% of that in maternal blood. The foetal arterio-venous ratio of remifentanyl concentrations was approximately 30%, suggesting metabolism of remifentanyl in the new born infant.

Remifentanyl should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

### Labour and delivery

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

For a summary of the reproductive toxicity study findings please refer to Section 5.3.

## 4.7 Effects on ability to drive and use machines

After anaesthesia with remifentanyl 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 remifentanyl are direct extensions of  $\mu$ -opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanyl administration.

The frequencies below are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) to very rare ( $< 1/10,000$ ).

### Immune System Disorders

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

### Nervous System Disorders

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

### Cardiac Disorders

Common:	Bradycardia
Rare:	Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanyl in conjunction with other anaesthetic agents.

### 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
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### General Disorders and Administration Site Conditions

Common:	Post-operative shivering
Uncommon:	Post-operative aches

## 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 Remifentanil, 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 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 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 Remifentanil is unlikely to exceed the duration of action of the opioid antagonist.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01A H06.

Remifentanil is a selective  $\mu$ -opioid agonist with a rapid onset and very short duration of action. The  $\mu$ -opioid activity of remifentanil is antagonised by narcotic antagonists, such as naloxone.

Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 $\mu$ g/kg.

#### Neonates/infants (aged less than 1 year):

In a randomised (ratio of 2:1, remifentanil:halothane), open label, parallel group, multicentre study in 60 young infants and neonates  $\leq 8$  weeks of age (mean 5.5 weeks) with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0.4  $\mu$ g/kg/min initial continuous infusion plus supplemental doses or infusion rate changes as needed) was compared with halothane (given at 0.4% with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 70% nitrous oxide (N<sub>2</sub>O) plus 30% oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant). Use for Total Intravenous anaesthesia (TIVA) - children aged 6 months to 16 years TIVA with remifentanil in paediatric surgery was compared to inhalation anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical intervention	Age (y), (N)	Study condition (maintenance)	Extubation (min)
Lower abdominal/urological surgery	0.5-16 (120)	TIVA: propofol (5 – 10 mg/kg/h) + remifentanyl (0.125 – 1.0 µg/kg/min)	11.8 (4.2)
		Inhalation anaesthesia: sevoflurane (1.0 – 1.5 MAC) and remifentanyl (0.125 – 1.0 µg/kg/min)	15.0 (5.6) (p<0.05)
ENT-surgery	4-11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanyl (0.5 µg/kg/min)	11 (3.7)
		Inhalation anaesthesia: desflurane (1.3 MAC) and N <sub>2</sub> O mixture	9.4 (2.9) Not significant
General or ENT surgery	2-12 (153)	TIVA: remifentanyl (0.2 – 0.5 µg/kg/min) + propofol (100 - 200 µg/kg/min)	Comparable extubation times (based on limited data)
		Inhalation anaesthesia: sevoflurane (1 – 1.5 MAC) + N <sub>2</sub> O mixture	

In the study in lower abdominal/urological surgery comparing remifentanyl/propofol with remifentanyl/sevoflurane, hypotension occurred significantly more often under remifentanyl/sevoflurane, and bradycardia occurred significantly more often under remifentanyl/propofol. In the study in ENT surgery comparing remifentanyl/propofol with desflurane/nitrous oxide, a significantly higher heart rate was seen in subjects receiving desflurane/nitrous oxide compared with remifentanyl/propofol and with baseline values.

5.2 Pharmacokinetic properties

Following administration of the recommended doses of remifentanyl, the effective half-life is 3 to 10 minutes. The average clearance of remifentanyl in young healthy adults is 40 ml/min/kg, the central volume of distribution is 100 ml/kg, and the steady-state volume of distribution is 350 ml/kg. Blood concentrations of remifentanyl are proportional to the dose administered throughout the recommended dose range. For every 0.1 µg/kg/min increase in infusion rate, the blood concentration of remifentanyl will rise 2.5 ng/ml. Remifentanyl is approximately 70% bound to plasma proteins.

Metabolism

Remifentanyl is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanyl results in the formation of a carboxylic acid metabolite, which in dogs is 1/4600th as potent as remifentanyl. Studies in man indicate that all pharmacological activity is associated with the parent compound. The activity of this metabolite is therefore not of any clinical consequence. The half-life of the metabolite in healthy adults is 2 hours. In patients with normal renal function, the time for 95% elimination of the primary metabolite of remifentanyl by the kidneys is approximately 7 to 10 hours. Remifentanyl is not a substrate for plasma cholinesterase.

Cardiac anaesthesia

The clearance of remifentanyl is reduced by approximately 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree centigrade.



## Renal impairment

The rapid recovery from remifentanyl-based sedation and analgesia is unaffected by renal status.

The pharmacokinetics of remifentanyl are not significantly changed in patients with varying degrees of renal impairment even after administration for up to 3 days in the intensive care setting.

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. In patients with anuria the half-life of the carboxylic acid metabolite is increased to 30 hours. In intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite is expected to reach approximately 100-fold the level of remifentanyl at steady-state. The available clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant  $\mu$ -opioid effects even after administration of remifentanyl infusions for up to 3 days in these patients. There are no data available on the safety and pharmacokinetic profile of the metabolite following infusions of Remifentanyl Mylan for durations greater than 3 days.

There is no evidence that remifentanyl is extracted during renal replacement therapy.

The carboxylic acid metabolite is extracted during haemodialysis by at least 30%.

## Hepatic impairment

The pharmacokinetics of remifentanyl are not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanyl.

These patients should be closely monitored and the dose of remifentanyl should be titrated to the individual patient need.

## Paediatric patients

The average clearance and steady state volume of distribution of remifentanyl are increased in children and decline to adolescents values by age 17. The values of these parameters in new born infants are approximately twice those of adolescents. The elimination half-life of remifentanyl in new born infants is not significantly different from that of adolescents. Changes in analgesic effect after changes in infusion rate of remifentanyl should be rapid and similar to those seen in adolescents. The pharmacokinetics of the carboxylic acid metabolite in children aged 2 to 11 years and adolescents aged 12 to 17 years are similar to those seen in adults after correcting for differences in body weight.

## Elderly

The clearance of remifentanyl is slightly reduced in elderly patients (>65 years) compared to young patients. The pharmacodynamic activity of remifentanyl increases with increasing age. Elderly patients have a remifentanyl  $EC_{50}$  for formation of delta waves on the electroencephalogram (EEG) that is 50% lower than young patients; therefore, the initial dose of remifentanyl should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

## 5.3 Preclinical safety data

Remifentanyl, like some other fentanyl analogues, produced increases in action potential duration (APD) in dog isolated Purkinje fibres.

There were no effects at a concentration of 0.1 micromolar (38 ng/ml). Effects were seen at a concentration of 1 micromolar (377 ng/ml), and were statistically significant at a concentration of 10 micromolar (3770 ng/mL).

These concentrations are 12-fold and 119-fold respectively the highest likely free concentrations (or 3-fold and 36-fold respectively, the highest likely whole blood concentrations) following the maximum recommended therapeutic dose.

## Acute toxicity

Expected signs of  $\mu$ -opioid intoxication were observed in non-ventilated mice, rats, and dogs after large single bolus intravenous doses of remifentanyl. In these studies, the most sensitive species, the male rat, survived following administration of 5 mg/kg. Hypoxia-induced brain microhaemorrhages observed in dogs were reversed within 14 days after completion of dosing.

**Repeat dose toxicity**

Bolus doses of remifentanyl administered to non-ventilated rats and dogs resulted in respiratory depression in all dose groups, and in reversible brain microhaemorrhages in dogs. Subsequent investigations showed that the microhaemorrhages resulted from hypoxia and were not specific to remifentanyl. Brain microhaemorrhages were not observed in infusion studies in nonventilated rats and dogs because these studies were conducted at doses that did not cause severe respiratory depression.

It is to be derived from preclinical studies that respiratory depression and associated sequelae are the most likely cause of potentially serious adverse events in humans.

Intrathecal administration to dogs of the glycine formulation alone (i.e. without remifentanyl) caused agitation, pain, and hind limb dysfunction and incoordination. 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 Remifentanyl Mylan formulation, this finding has no clinical relevance for intravenous administration of Remifentanyl Mylan.

**Reproductive toxicity studies**

Remifentanyl reduced fertility in male rats after daily injection for at least 70 days. A no-effect dose was not demonstrated. Fertility was not affected in female rats. Teratogenic effects were not seen in rats or rabbits. Administration of remifentanyl to rats throughout late gestation and lactation did not significantly affect the survival, development, or reproductive performance of the F<sub>1</sub> generation.

*Placental and milk transfer*

Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanyl and/or its metabolites during growth and development. Remifentanyl-related material is transferred to the milk of lactating rats. In a human clinical trial, the concentration of remifentanyl in foetal blood was approximately 50% of that in maternal blood. The foetal arterio-venous ratio of remifentanyl concentrations was approximately 30%, suggesting metabolism of remifentanyl in the new born infant.

**Genotoxicity**

Remifentanyl did not yield positive findings in a series of *in vitro* and *in vivo* genotoxicity tests, except in the *in vitro* mouse lymphoma tk assay, which gave a positive result with metabolic activation. Since the mouse lymphoma results could not be confirmed in further *in vitro* and *in vivo* tests, treatment with remifentanyl is not considered to pose a genotoxic hazard to patients.

**Carcinogenicity**

Long-term carcinogenicity studies were not performed.

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Glycine.  
Hydrochloric acid 37% (for pH adjustment).

**6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal product except those mentioned in section 6.6. It should not be admixed with lactated Ringer's solution for injection or lactated Ringer's and glucose 50 mg/ml (5%) solution for injection. Remifentanyl should not be mixed with propofol in the same intravenous admixture solution.

Administration of Remifentanyl into the same intravenous line with blood/serum/plasma is not recommended as non-specific esterase in blood products may lead to the hydrolysis of remifentanyl to its inactive metabolite.

Remifentanyl should not be mixed with other therapeutic agents prior to administration.

### 6.3 Shelf life

3 years

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25° C.

Chemical and physical-in-use stability of the diluted solution has been demonstrated for 4 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

5 ml vial (type I colourless glass) of remifentanyl 2 mg with a chlorobutyl stopper and a flip-off cap.

Packs of 1, 5, 10, 20, 25 and 50 vials.

Not all pack sizes may be marketed

### 6.6 Special precautions for disposal and other handling

Remifentanyl should be prepared for intravenous use by adding 2ml of diluent to give a reconstituted solution with a concentration of 1mg/ml remifentanyl.

The reconstituted solution is clear, colourless, and practically free from particulate material.

After reconstitution, visually inspect the product (where the container permits) for particulate material, discolouration or damage of container. Discard any solution where such defects are observed. Reconstituted product is for single use only. Any unused material should be discarded.

Remifentanyl should not be administered by manually-controlled infusion without further dilution to concentrations of 20 to 250 µg/ml (50 µg/ml is the recommended dilution for adults and 20 to 25 µg/ml in paediatric patients aged 1 year and over).

Remifentanyl should not be administered by TCI without further dilution (20 to 50 µg/ml is the recommended dilution for TCI).

The dilution is dependent upon the technical capability of the infusion device and the anticipated requirements of the patient.

One of the following I.V. fluids listed below should be used for dilution:

- Water for injections
- Glucose 50 mg/ml (5 %) solution for injection,
- Glucose 50 mg/ml (5 %) and sodium chloride 9 mg/ml (0.9%) solution for injection,
- Sodium chloride 9 mg/ml (0.9 %) solution for injection,
- Sodium chloride 4.5 mg/ml (0.45 %) solution for injection.

After dilution, visually inspect the product to ensure it is clear, colourless, practically free from particulate matter and the container is undamaged. Discard any solution where such defects are observed.

Any unused product or waste material should be disposed of in accordance with local requirements.

Remifentanyl has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter:

- Lactated Ringer's solution for injection,
- Lactated Ringer's and glucose 50 mg/ml (5 %) solution for injection.

Remifentanyl has been shown to be compatible with propofol when administered into a running IV catheter.

## **7 MARKETING AUTHORISATION HOLDER**

Generics (UK) Ltd  
Station Close  
Potters Bar  
Hertfordshire  
EN6 1TL  
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## **8 MARKETING AUTHORISATION NUMBER**

PA 405/57/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 7 May 2010

Date of last renewal: 31 January 2012

## **10 DATE OF REVISION OF THE TEXT**

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