Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Remifentanil Teva 5 mg Powder for Concentrate for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains remifentanil hydrochloride equivalent to 5 mg remifentanil.

Each ml of Remifentanil Teva 5 mg Powder for Concentrate for Solution for Injection or Infusion contains 1 mg remifentanil when reconstituted as directed.

Excipients:

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free':

Each 5 mg vial of powder for concentrate for solution for injection or infusion contains 0 - 0.064 mmol (0 - 1.47 mg) sodium.

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 or yellowish, compact powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Remifentanil Teva is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia.

Remifentanil Teva 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

Remifentanil should 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 patient airway and assisted ventilation.

Continuous infusions of remifentanil 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 to minimise the potential dead space (see section 6.6 for additional information and section 4.2.5 for tables with examples of infusion rates by body weight to help titrate remifentanil to the patients anaesthetic needs).

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual remifentanil after use (see section 4.4). IV lines/infusion system should be removed after cessation of use to avoid inadvertent administration.

Remifentanil may 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).

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

Dilution

Remifentanil should not be administered without further dilution after reconstitution of the lyophilised powder. See section 6.3 for storage conditions and section 6.6 for recommended diluents and instructions on reconstitution/dilution of the product before administration

4.2.1 General Anaesthesia
The administration of remifentanil must be individualised based on the patient's response.

4.2.1.1 Adults

Administration by Manually Controlled Infusion (MCI)

Table 1: Dosing Guidelines for Adults

	REMIFENTANIL BOLUS INJECTION (µg/kg)	**CONTINUOUS REMIFENTANIL INFUSION (µg/kg/min)**	
		Starting Rate	**Range**
	Induction of anaesthesia		
	1 (give over not less than 30 sec.)	0.5 to 1	-
Concomitant anaesthetic agent	**Maintenance of anaesthesia in ventilated patients**		
• Nitrous oxide (66%)	0.5 to 1	0.4	0.1 to 2
• Isoflurane (starting dose 0.5 MAC)	0.5 to 1	0.25	0.05 to 2
• Propofol (starting dose 100 µg/kg/min)	0.5 to 1	0.25	0.05 to 2

When given by bolus injection at induction remifentanil should 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 (hypotension and bradycardia) of remifentanil.

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
Remifentanil should be administered with a hypnotic agent, such as propofol, thiopentone, or isoflurane, for the induction of anaesthesia. Administering remifentanil after a hypnotic agent will reduce the incidence of muscle rigidity. Remifentanil can be administered at an infusion rate of 0.5 to 1 µg/kg/min, with or without an initial 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 remifentanil, then a bolus injection is not necessary.

Maintenance of anaesthesia in ventilated patients
After endotracheal intubation, the infusion rate of remifentanil should be decreased, according to anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of remifentanil, 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 bolus injections may be administered every 2 to 5 minutes.

Anaesthesia in spontaneously breathing anaesthetised patients with a secure airway (e.g. laryngeal mask anaesthesia):
In spontaneously breathing anaesthetised patients with a secured airway respiratory depression is likely to occur. Therefore attention must be given to respiratory effects eventually combined with muscle rigidity. Special care is needed to adjust the dose to the patient requirements and ventilatory support may be required. Adequate facilities should be available for monitoring of patients who have been administered remifentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression (intubation equipment must be available) and/or muscle rigidity (for more information 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.

Remifentanil 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 inhalation 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 during immediate post-operative period
Due to the very rapid offset of action of remifentanil 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 remifentanil. 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 case the longer acting analgesic has not reached the appropriate effect before the end of surgery, the administration of remifentanil can be continued to maintain analgesia during immediate postoperative period until the longer acting analgesic has reached the maximum effect.

If remifentanil is continued post-procedure, it 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. Furthermore, it is recommended that patients should be closely monitored post-operatively for pain, hypotension and bradycardia.

Further information about the administration in mechanically ventilated intensive care patients is given in section 4.2.3.

In spontaneously breathing patients the initial infusion rate of remifentanil may be decreased to 0.1 μg/kg/min and thereafter can be increased or reduced every 5 min in steps of 0.025 μg/kg/min to balance the extent of analgesia against the degree of respiratory depression.

In spontaneously breathing patients bolus doses for analgesia are not recommended during the postoperative period.

Administration by target-controlled infusion (TCI)

Induction and maintenance of anaesthesia in ventilated patients
Remifentanil 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 1 above for manually controlled infusion). 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. Remifentanil should be titrated to the 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 (hypotension and bradycardia) of remifentanil (see table 1 above for manually controlled infusion).

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

Table 2. Remifentanil blood concentrations (nanograms/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 (micrograms/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

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 also *Guidelines for discontinuation/continuation during immediate post-operative period* in section above for *Manually Controlled Infusion*).

As there are insufficient data, the administration of remifentanil 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 remifentanil with induction agents has not been studied.

The use of remifentanil for induction of anaesthesia by TCI in patients aged 1 to 12 years is not recommended as there are no data available in this patient population.

Maintenance of anaesthesia
The following doses of remifentanil (see table 3) are recommended for maintenance of anaesthesia:

Table 3: Dosing Guideline for Paediatric Patients (1 to 12 years of age)

*CONCOMITANT ANAESTHETIC AGENT	REMIFENTANIL BOLUS INJECTION (µg/kg)	CONTINUOUS REMIFENTANIL INFUSION (µg/kg/min)	
		Starting Rate	Maintenance Rate
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 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 exclusive administration of nitrous oxide (70%) remifentanil infusion rates for the maintenance of anaesthesia should be between 0.4 and 3 µg/kg/min. Data gained from adults suggest that 0.4 µg/kg/min may be a convenient initial dose although specific studies are lacking.

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 (hypotension and bradycardia) of remifentanil. No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil (see in section above: *Administration by Manually Controlled Infusion (MCI), Concomitant medication*).

Guidelines for patient management in the immediate post-operative period/Establishment of alternative analgesia prior to discontinuation of remifentanil:
Due to the very rapid offset of action of remifentanil, 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 remifentanil. 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 and infants (aged less than 1 year)

The pharmacokinetic profile of remifentanil in neonates and infants (aged less than 1 year (see section 5.1)) 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 remifentanil is not recommended for this age group.

Use for Total Intravenous anaesthesia (TIVA): There is limited clinical trial experience of remifentanil of TIVA in infants (see section 5.1). However, there are insufficient clinical data to make dosage recommendations.

4.2.1.4 Special patient groups

For dosage recommendations for special patient groups (elderly and obese patients, renally and hepatically impaired patients, patients undergoing neurosurgery and ASA III/IV patients) see section 4.2.4.

4.2.2 Cardiac Surgery

Administration by Manually Controlled Infusion

For dosage recommendations in patients undergoing cardiac surgery see table 4 below:

Table 4: Dosing Guidelines for Cardiac Anaesthesia

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

Induction period of anaesthesia
After administration of hypnotic to achieve loss of consciousness, remifentanil should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus injections of remifentanil 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 remifentanil should be titrated according to patient need. Supplemental bolus doses may also be given as required. High risk cardiac patients, such as those undergoing valve surgery or with poor left ventricular function, 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, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid increase of haemodynamic effects (hypotension and bradycardia) of remifentanil. No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil (see in section above: *Administration by Manually Controlled Infusion (MCI), Concomitant medication*).

Guidelines for post-operative supply of patient
Continuation of remifentanil post-operatively to provide analgesia prior to extubation
It is recommended that the infusion of remifentanil 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 remifentanil infusion rate adjusted to meet the individual patient's requirements (for further information on management of intensive care patients see section 4.2.3).

Establishment of alternative analgesia prior to discontinuation of remifentanil
Due to the very rapid offset of action of remifentanil, no residual opioid activity will be present within 5 to 10 minutes after discontinuation. Prior to discontinuation of remifentanil, 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 remifentanil
Due to the very rapid offset of action of remifentanil, hypertension, shivering and pain have been reported in cardiac patients immediately following discontinuation of remifentanil (see section 4.8). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the remifentanil infusion is discontinued. The infusion rate should be reduced by 25% decrements in at least 10-minute intervals until the infusion is discontinued.

During the weaning from the ventilator the remifentanil 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 opioids are administered as part of the regimen for transition to alternative analgesia, the patient must be carefully monitored. The benefit of providing appropriate post-operative analgesia must always be balanced against the potential risk of respiratory depression of these products.

Administration by Target-Controlled Infusion

Induction and maintenance of anaesthesia
Remifentanil 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 4 *Dosing Guidelines for Cardiac Anaesthesia* 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 (hypotension and bradycardia) of remifentanil (see table 4 *Dosing Guidelines for Cardiac Anaesthesia* above).

For information on blood remifentanil concentrations achieved with manually controlled infusion see table 2, *Remifentanil blood concentrations (ng/ml) estimated using the Minto Model (1997)* in section 4.2.1.1.

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 of remifentanil* in section 4.2.1.1).

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

4.2.3 Intensive Care

4.2.3.1 Adults
Remifentanil can be used for the provision of analgesia in mechanically ventilated intensive care patients. If required, additionally sedating drugs should be applied.

Remifentanil has been studied in intensive care patients in well controlled clinical trials for up to three days. As patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore a usage of longer than three days is not recommended.

Due to the lack of data the administration of remifentanil by TCI is not recommended for ICU patients.

In adults, it is recommended that remifentanil 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 sedation and analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The level of sedation and analgesia should be carefully monitored, regularly reassessed and the remifentanil infusion rate adjusted accordingly. If an infusion rate of 0.2 μg/kg/min (12 μg/kg/h) is reached and the desired level of sedation is not achieved, 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 remifentanil 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 and sedation in individual patients:

Table 5: Dosing guidelines for use of remifentanil within the intensive care setting

CONTINUOUS REMIFENTANIL INFUSION μg/kg/min (μg/kg/h)	
Starting Rate	**Range**
0.1 (6) to 0.15 (9)	0.006 (0.38) to 0.74 (44.4)

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

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

Table 6: Recommended starting dose of sedative agents, if required

Sedative Agent	**Bolus (mg/kg)**	**Infusion rate (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 painful procedures
An increase in the existing remifentanil 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 remifentanil 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%-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 analgesia during stimulating painful procedures.

Establishment of alternative analgesia prior to discontinuation of remifentanil
Due to the very rapid offset of action of remifentanil, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. After administration of remifentanil the potential for the development of tolerance and hyperalgesia should be attended. Therefore, prior to discontinuation of remifentanil, 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 and to prevent hyperalgesia and concomitant haemodynamic changes. It is therefore recommended that the choice of agent(s), the dose and the time of administration are planned prior to discontinuation of remifentanil. Long-acting analgetics or intravenous or local analgetics, which can be controlled by the health care staff or the patient are alternative options for analgesia and should be chosen carefully according to the patient needs.

Prolonged administration of μ-opioid agonists may induce development of tolerance.

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

Upon discontinuation of remifentanil, 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.

4.2.3.2 Paediatric intensive care patients

The use of remifentanil in paediatric intensive care patients cannot be recommended as there are no data available in this patient population.

4.2.3.3 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 carboxylic acid metabolite is reduced in patients with impaired renal function (see section 5.2).

4.2.4 Special patient groups

4.2.4.1 Elderly (over 65 years of age)

General anaesthesia
Caution should be exercised in the administration of remifentanil in this population. The initial starting dose of remifentanil administered to patients over 65 should be half the recommended adult dose and then titrated to individual patient's need as an increased sensitivity to the pharmacodynamic effects of remifentanil has been seen in this patient population. This dosage adjustment refers to application during all phases of anaesthesia including induction, maintenance and immediate post-operative analgesia.

Because of the increased sensitivity of elderly patients to remifentanil, when administering remifentanil by TCI in this population the initial target concentration should be 1.5 to 4 ng/ml with subsequent titration according to the individual patients response.

Anaesthesia during cardiac surgery
Reduction of initial dosage is not required (see section 4.2.2).

Intensive care
Reduction of initial dosage is not required (see section *Intensive Care* above).

4.2.4.2 Obese patients

For manually controlled infusion it is recommended that for obese patients the dosage of remifentanil 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/m^2 and in male patients with BMI greater than 40 kg/m^2. To avoid underdosing in these patients, remifentanil TCI should be titrated carefully to individual response.

4.2.4.3 Renally impaired patients

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; however, these patients exhibit reduced clearance of carboxylic acid metabolite.

4.2.4.4 Patients with hepatic impairment

No adjustment of the initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of remifentanil is unchanged in this patient population. However, patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil (see section 4.4). These patients should be closely monitored and the dose of remifentanil titrated to individual patient need.

4.2.4.5 Neurosurgery patients

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 remifentanil in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

As there are insufficient data, dosage recommendation cannot be given for children. 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).

4.2.5 Guidelines for infusion rates of remifentanil for manually controlled infusion

Table 7: Remifentanil infusion rates (ml/kg/h)

Drug Delivery Rate	**Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of**			
(µg/kg/min)	**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 8: Remifentanil infusion rates (ml/h) for a 20 µg/ml solution

Infusion Rate	**Patient Weight (kg)**						
(µg/kg/min)	**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 9: Remifentanil infusion rates (ml/h) for a 25 µg/ml solution

Infusion Rate	**Patient Weight (kg)**									
(µg/kg/min)	**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 10: Remifentanil infusion rates (ml/h) for a 50 µg/ml solution

Infusion Rate	**Patient Weight (kg)**							
(µg/kg/min)	**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 11: Remifentanil infusion rates (ml/h) for a 250 µg/ml solution

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

4.3 Contraindications

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

Remifentanil Teva is contra-indicated in patients with hypersensitivity to remifentanil and other fentanyl analogues or to any of the excipients.

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

4.4 Special warnings and precautions for use

Remifentanil should 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. As mechanically ventilated, intensive care patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore, a longer usage is not recommended in intensive care patients.

Rapid offset of action
Due to the very rapid offset of action of remifentanil, patients may emerge rapidly from anaesthesia and no residual opioid activity will be present within 5-10 minutes after the discontinuation of remifentanil. During administration of remifentanil as a μ-opioid agonist the potential for the development of tolerance and hyperalgesia should be paid attention to. Therefore, prior to discontinuation of remifentanil, 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 and to prevent hyperalgesia and concomitant haemodynamic changes. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of remifentanil. 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. 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 Remifentanil Teva 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, bolus injections should 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 including ventilatory support. 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 a μ-opioid antagonist may be administered; however this may reverse or attenuate the analgesic effect of remifentanil.

Respiratory depression – preventive measures and treatment
As with all potent opioids, profound analgesia is accompanied by marked respiratory depression. Therefore, remifentanil should only be used in areas where facilities for monitoring and dealing with respiratory depression are available. Special care should be taken in patients with impaired lung function and with severe hepatic impairment. These patients may be slightly more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored and the dose of remifentanil titrated to individual patient need.

The appearance of respiratory depression should be managed appropriately, including decreasing the rate of infusion by 50%, or by 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 in the presence of confounding factors (e.g. inadvertent administration of bolus doses (see section below) and administration of concomitant longer acting opioids), respiratory depression occurring up to 50 minutes after discontinuation of infusion has been reported. 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
Hypotension and bradycardia can give rise to asystole and cardiac arrest (see section 4.5 and 4.8) may be managed by reducing the rate of infusion of remifentanil or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate.

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

Inadvertent administration
A sufficient amount of remifentanil 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 remifentanil into a fast flowing IV line or via a dedicated IV line which is removed when remifentanil is discontinued.

Neonates and infants
Up to now, conclusive data on neonates and infants younger than 1 year are lacking.

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 amounts or doses of inhalation 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 remifentanil (hypotension and bradycardia), may exacerbate in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents (see also sections 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies from the use of remifentanil in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3). Teratogenic effects were not seen in rats or rabbits. The potential risk for humans is unknown. Therefore, Remifentanil Teva should not be used in pregnancy unless clearly necessary.

The safety profile of remifentanil during labour or delivery has not been demonstrated. There are insufficient data to recommend remifentanil for use during labour and Caesarean section. Remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

Breast-feeding
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, caution should be exercised and nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of remifentanil.

4.7 Effects on ability to drive and use machines

Remifentanil has a major influence on the ability to drive and use machines. If an early discharge is envisaged after application of remifentanil, following treatment using anaesthetic agents, patients should be advised not to drive or operate machinery. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

4.8 Undesirable effects

The most common adverse events associated with remifentanil are direct extensions of μ-opioid agonist activities. The following terminologies have been used in order to classify the occurrence of undesirable effects:

Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to <1/100
Rarely ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000
not known (cannot be estimated from the available data).

Incidence is listed below within each body system:

Immune system disorders	
Rare:	hypersensitivity reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents
Psychiatric disorders	
Not known:	dependence
Nervous system disorders	
Very common:	skeletal muscle rigidity
Rare:	sedation (during awakening after general anaesthesia)
Cardiac disorders	
Common:	bradycardia
Rare:	asystole/cardiac arrest with preceding bradycardia in patients treated with remifentanil in combination with other anaesthetics
Vascular disorders	
Very common:	hypotension
Common:	post-operatively occurring 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:	pruritis
General disorders and administration site conditions	
Common:	post-operative shivering
Uncommon:	post-operative pain

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 is 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, the following actions should be taken: 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 agents 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 in addition to ventilatory support to manage severe respiratory depression. 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 μ-opioid agonist with a rapid onset and very short duration of action. The μ-opioid activity, of remifentanil, is antagonised by narcotic antagonists, such as naloxone.
Assays of histamine in patients and healthy volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 μg/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 ≤ 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 μg/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_20) 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 remifenanil 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) (mean (SD))
Lower abdominal/urological surgery	0.5-16 (120)	TIVA: propofol (5 - 10 mg/kg/h) + remifentanil (0.125 - 1.0 μg/kg/min) Inhalation anaesthesia: sevoflurane (1.0 - 1.5 MAC) and remifentanil (0.125 - 1.0 μg/kg/min)	11.8 (4.2) 15.0 (5.6) (p<0.05)
ENT-surgery	4-11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0.5 μg/kg/min) Inhalation anaesthesia: desflurane (1.3 MAC) and	11 (3.7) 9.4 (2.9) Not significant

		N_2O mixture	
General or ENT surgery	2-12 (153)	TIVA: remifentanil (0.2 - 0.5 µg/kg/min) + propofol (100 - 200 µg/kg/min) Inhalation anaesthesia: sevoflurane (1 - 1.5 MAC) + N_2O mixture	Comparable extubation times (based on limited data)

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

5.2 Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes. The average clearance of remifentanil 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 remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 µg/kg/min increase in i.v. infusion rate, the blood concentration of remifentanil will rise 2.5 ng/ml. Remifentanil is approximately 70% bound to plasma proteins.

Metabolism
Remifentanil is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite (1/4600th as potent as remifentanil). 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. Approximately 95% of remifentanil as the carboxylic acid metabolite is recovered in the urine in patients with normal renal function. Remifentanil is not a substrate for plasma cholinesterase.

Placental and milk transfer
In a human clinical trial, the average maternal remifentanil concentrations were approximately twice those seen in the foetus. In some cases, however, foetal concentrations were similar to those in the mother. The umbilical arteriovenous ratio of the remifentanil concentration was approximately 30% suggesting metabolism of remifentanil in the neonate. Remifentanil related material is transferred to the milk of lactating rats.

Cardiac anaesthesia
The clearance of remifentanil 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 remifentanil-based sedation and analgesia is unaffected by renal status.
The pharmacokinetics of remifentanil 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 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 remifentanil at steady-state. Clinical data demonstrate that the accumulation of the metabolite does not result in clinically relevant µ-opioid effects even after administration of remifentanil infusions for up to 3 days in these patients. Up to now, data on safety and pharmacokinetic activity of metabolites after infusion of remifentanil for more than 3 days are lacking.

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

The carboxylic acid metabolite is extracted during haemodialysis by 25 - 35 %. In patients with anuria the half-life of the carboxylic acid metabolite is increased to 30 hours.

Hepatic impairment
The pharmacokinetics of remifentanil 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 remifentanil. These patients should be closely monitored and the dose of remifentanil should be titrated to the individual patient need.

Paediatric patients
The average clearance and steady state volume of distribution of remifentanil are increased in younger children and decline to young healthy adult values by age 17. The elimination half-life of remifentanil in neonates is not significantly different from that of young healthy adults. Changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to those seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 and 17 years of age are similar to those seen in adults after correcting for differences in body weight.

Elderly
The clearance of remifentanil is slightly reduced (approximately 25%) in elderly patients (over 65 years of age) compared to that in young patients. The pharmacodynamic activity of remifentanil increases with increasing age. Elderly patients have a remifentanil EC50 for formation of delta waves on the electroencephalogram that is 50% lower than young patients; therefore, the initial dose of remifentanil should be reduced by 50% in elderly patients and then carefully titrated to meet the individual patient need.

5.3 Preclinical safety data

Acute toxicity
Expected signs of μ-opioid intoxication were observed in non-ventilated mice, rats, and dogs after large single bolus intravenous doses of remifentanil. In these studies, the most sensitive species, the male rat, survived following administration of 5 mg/kg.
Intracranial bleedings in dogs caused by hypoxia declined within 14 days after stopping remifentanil application.

Chronic toxicity
Bolus doses of remifentanil administered to non-ventilated rats and dogs resulted in respiratory depression in all dose groups, and in reversible intracranial bleedings in dogs. Subsequent investigations showed that the microhaemorrhages resulted from hypoxia and were not specific to remifentanil. Brain microhaemorrhages were not observed in infusion studies in non-ventilated 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 remifentanil) evoked 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 Remifentanil Teva formulation, this finding has no clinical relevance for intravenous administration of Remifentanil Teva.

Reproductive toxicity studies
Placental transfer studies in rats and rabbits showed that pups are exposed to remifentanil and/or its metabolites during growth and development. Remifentanil-related material is transferred to the milk of lactating rats.

Remifentanil has been shown to reduce fertility in male rats when administered daily by intravenous injection for at least 70 days at a dose of 0.5 mg/kg, or approximately 250 times the maximum recommended human bolus dose of 2 microgram/kg. The fertility of female rats was not affected at doses up to 1 mg/kg when administered for at least 15 days prior to mating. No teratogenic effects have been observed with remifentanil at doses up to 5 mg/kg in rats and 0.8 mg/kg in rabbits. Administration of remifentanil to rats throughout late gestation and lactation at doses up to 5 mg/kg IV had no significant effect on the survival, development, or reproductive performance of the F1 generation.

Genotoxicity
Remifentanil 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 remifentanil is not considered to pose a genotoxic hazard to patients.

Carcinogenicity
Long term animal carcinogenicity studies have not been performed with remifentanil.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine (E640)
Hydrochloric acid (E507), for pH-adjustment
Sodium hydroxide (E524), for pH-adjustment

6.2 Incompatibilities

Remifentanil Teva must not be mixed with other medicinal products except those mentioned in section 6.6.

It should not be admixed with Lactated Ringer's Injection, Lactated Ringer's and glucose 50 mg/ml (5%) solution for injection.

Remifentanil Teva should not be mixed with propofol in the same intravenous admixture solution. For compatibility when given into a running i.v. catheter, please see section 6.6.

Administration of Remifentanil Teva 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 remifentanil to its inactive metabolite.

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

6.3 Shelf life

As packaged for sale:
2 years

After reconstitution/dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C after initial reconstitution with:
- Water for injections
- Glucose 50 mg/ml (5%) solution for injection
- Glucose 50 mg/ml (5%) solution for injection 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
- Lactated Ringer's Injection
- Lactated Ringer's and glucose 50 mg/ml (5%) solution for injection

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C after further dilution with:
- Water for injections
- Glucose 50 mg/ml (5%) solution for injection
- Glucose 50 mg/ml (5%) solution for injection 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

Chemical and physical in-use stability has been demonstrated for 8 hours at 25°C after further dilution with:
- Lactated Ringer's Injection
- Lactated Ringer's and glucose 50 mg/ml (5%) solution for injection

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.

Any unused portion should be discarded.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

12.5 ml vials of colourless type I glass with bromobutyl rubber stopper and blue cap.

Pack sizes: 1 or 5 vials per pack

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution:
Remifentanil Teva should be prepared for intravenous use by adding the appropriate volume (as stated in the table below) of one of the below listed diluents to give a reconstituted solution with a concentration of approximately 1 mg/ml.

Presentation	**Volume of diluent to be added**	**Concentration of the reconstituted solution**
Remifentanil Teva 1 mg	1 ml	1 mg/ml
Remifentanil Teva 2 mg	2 ml	1 mg/ml
Remifentanil Teva 5 mg	5 ml	1 mg/ml

Shake until completely dissolved. The reconstituted solution should be clear, colourless and free of visible particles.

Further Dilution:
After reconstitution, Remifentanil Teva 5 mg should not be administered 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 for paediatric patients aged 1 year and over) with one of the following IV fluids listed below.

For target-controlled infusion (TCI) the recommended dilution of Remifentanil Teva is 20 to 50 µg/ml.
The dilution is dependent on the technical capability of the infusion device and the anticipated requirements of the patient.

One of the following solutions should be used for dilution:
- Water for injections
- Glucose 50 mg/ml (5%) solution for injection
- Glucose 50 mg/ml (5%) solution for injection 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

The following intravenous fluids may also be used when administered into a running IV catheter:
- Lactated Ringer's Injection
- Lactated Ringer's and glucose 50 mg/ml (5%) solution for injection

Remifentanil Teva is compatible with propofol when administered into a running IV catheter.

No other diluents should be used.
The solution is to be inspected visually for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles.

Ideally, intravenous infusions of remifentanil should be prepared at the time of administration (see section 6.3).
The content of the vial is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/98/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th February 2011

Date of last renewal: 31st January 2012

10 DATE OF REVISION OF THE TEXT

November 2012