Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Remifentanil 2mg powder for concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Remifentanil 2 mg powder for concentrate for solution for injection/infusion
1 vial contains 2 mg remifentanil (as remifentanil hydrochloride).

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

Excipient with known effect: sodium 1.15 mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for injection/infusion
Lyophilized white to slightly yellow cake or powdery mass.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Remifentanil is indicated for provision of analgesia in mechanically ventilated intensive care patients of 18 years of age and older.

4.2 Posology and method of administration

Posology

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

Adults
Administration by manually-controlled infusion (MCI)

Dosing guidelines for adults

	REMIFENTANIL BOLUS INJECTION (micrograms /kg)	REMIFENTANIL CONTINUOUS INFUSION (micrograms/kg/min)	
		Starting Rate	Range
	1 (within at least 30 seconds)	0.5 to 1	_
	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 microtrams /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 co-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 micrograms/kg/min, with or without an initial bolus injection of 1 micrograms/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 patients
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 muscular 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 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 inhalational anaesthetics, hypnotics and benzodiazepines required for anaesthesia (see section 4.5).
Doses of the following agents used in anaesthesia: isoflurane, thiopentone, propofol and temazepam have been reduced by up to 75 % when used concurrently with remifentanil.

Guidelines for discontinuation/continuation during immediate postoperative 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-procedural, 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 this section.
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 decreased 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 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 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 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:
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 (micrograms/kg/min)	Remifentanil Blood Concentration (nanograms/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 postoperative 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.

Paediatric population

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.

Maintenance of anaesthesia
The following doses of remifentanil (see table) are recommended for maintenance of anaesthesia:
Dosing guidelines for paediatric patients (1 to12 years of age)

*concomitant anaesthetic agent	Remifentanil bolus injection (micrograms/kg)	Remifentanil continuous infusion	
		Starting Rate (micrograms/kg/min)	Range for maintenance of anaesthesia (micrograms/kg/min)
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 exclusive administration of nitrous oxide (70 %) and Remifentanil infusion rates for maintenance of anaesthesia should be between 0.4 und 3 micrograms/kg/min. Data gained from adults suggest that 0.4 micrograms/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).

Neonates/infants (aged less than 1 year)
There is limited clinical trial experience of remifentanil in neonates and infants (aged under 1 year old; see section 5.1). The pharmacokinetic profile of remifentanil in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction for body weight differences (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 for TIVA in infants (see section 5.1). However, there are insufficient clinical data to make dosage recommendations.

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 below).

Cardiac Surgery
Administration by Manually-Controlled Infusion
For dosage recommendations in patients undergoing cardiac surgery see table below:

Dosing guidelines for cardiac anaesthesia

INDICATION	REMIFENTANIL BOLUS INJECTION (micrograms /kg)	REMIFENTANIL CONTINUOUS INFUSION (micrograms /kg/min)	
		Starting Rate	Typical infusion rates
Intubation	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 micrograms /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

Induction of anaesthesia

After administration of hypnotic to achieve loss of consciousness, Remifentanil should be administered at an initial infusion rate of 1 micrograms/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 the patient need. Supplemental bolus doses may also be administered 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 micrograms/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 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 postoperative supply of patient
Continuation of Remifentanil post-operatively to provide analgesia prior to extubation: It is recommended that the infusion of Remifentanil is maintained at the final intra-operative rate during transfer of patients to the post-operative care 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 (see Intensive care, below, for further information on management of intensive care patients.

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 aches have been reported in cardiac patients immediately following discontinuation of Remifentanil (see section 4.8). To minimise the risk of these events, 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 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 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 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 the table under Cardiac surgery/Administration by Manually-Controlled Infusion/Dosing guidelines for 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 remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 nanograms/ml have been achieved 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 under Cardiac surgery/Administration by Manually-Controlled Infusion/Dosing guidelines for cardiac anaesthesia).

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

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

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

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

Intensive Care

Adults

Remifentanil can be used 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 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 micrograms/kg/min (6 micrograms/kg/h) to 0.15 micrograms/kg/min (9 micrograms/kg/h). The infusion rate should be titrated in increments of 0.025 micrograms/kg/min (1.5 micrograms/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 carefully monitored, regularly reassessed and the Remifentanil infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min (12 micrograms/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 the sedative agent should be titrated to obtain the desired level of sedation. Further increases to the Remifentanil infusion rate in increments of 0.025 micrograms/kg/min (1.5 micrograms/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 remifentanil within the intensive care setting

CONTINUOUS INFUSION micrograms /kg/min (micrograms /kg/h)	
Starting Rate	Range
0.1 (6) to 0.15 (9)	0.006 (0.36) 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.

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 micrograms/kg/min (6 micrograms/kg/h) is

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 micrograms/kg/min (15 micrograms/kg/h), maximum 0.75 microgramskg/min (44,4 micrograms/kg/h), has been administered for provision of additional analgesia during stimulating 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 patients 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 gradually to 0.1 micrograms/kg/min (6 micrograms/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.

The following tables 1-5 give guidelines for infusion rates of Remifentanil for manually-controlled infusion:

Table 1: Remifentanil – Infusion rates (ml/kg/h)

Medicinal product delivery rate (μg/kg/min)	Infusion delivery rate (ml/kg/h) for solution concentrations of			
	20 micrograms/ml 1 mg/50 ml	25 micrograms/ml 1 mg/40 ml	50 micrograms/ml 1 mg/20 ml	250 micrograms/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 0.012
0.05	0.15	0.12	0.06	0.018
0.075	0.23	0.18	0.09	0.024
0.1	0.3	0.24	0.12	0.036
0.15	0.45	0.36	0.18	0.048
0.2	0.6	0.48	0.24	0.06
0.25	0.75	0.6	0.3	0.12
0.5	1.5	1.2	0.6	0.18
0.75	2.25	1.8	0.9	0.24
1.0	3.0	2.4	1.2	0.3
1.25	3.75	3.0	1.5	0.36
1.5	4.5	3.6	1.8	0.42
1.75	5.25	4.2	2.1	0.48
2.0	6.0	4.8	2.4	

Table 2: Remifentanil – Infusion rates (ml/h) for a 20 micrograms/ml solution

Infusion rate	Patient weight (kg)						
(micrograms/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 3: Remifentanil – Infusion rates (ml/h) for a 25 micrograms/ml solution

Infusion rate	Patient weight (kg)									
(micrograms/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
0.075	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	.0
0.1	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	18
0.15	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	.0
0.2	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4	43.2	24
										.0
										36
										.0
										48
										.0

Table 4: Remifentanil – Infusion rates (ml/h) for a 50 micrograms/ml solution

Infusion rate	Patient weight (kg)							
(micrograms/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 5: Remifentanil – Infusion rates (ml/h) for a 250 micrograms/ml solution

Infusion rate	Patient weight (kg)							
(micrograms/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

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 (micrograms/kg/min) at Steady State.

Remifentanil-Infusion rates (micrograms/kg/min)	Remifentanil-blood concentration (nanograms/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

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

Renally impaired
No adjustments to the doses recommended above are necessary in renally-impaired patients, including those undergoing renal replacement therapy. It should, however, be considered that in patients with impaired renal function the clearance of the carboxylic acid metabolite is reduced (see section 5.2).

Special patient groups

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 the individual patient's need as an increased sensitivity to the pharmacodynamic effects of remifentanil has been seen in this patient population. This dose adjustment refers to the use in all phases of the anaesthesia including onset, maintaining 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 nanogram/ml with subsequent titration according to the individual patient's response.

Anaesthesia in cardiac surgery
Reduction of initial dosage is not required.

Intensive care
Reduction of initial dosage is not required.

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 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.

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/m2 and in male patients with BMI greater than 40 kg/m2. To avoid underdosing in these patients, remifentanil TCI should be titrated carefully to individual response.

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

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.

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 patent 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, including tables with examples of infusion rates by body weight to help titrate remifentanil to the patient's 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).

Congestion of the infusion drips or tearing off should be avoided, and the infusion drips should be sufficiently rinsed in order to remove residual Remifentanil after discontinuation of medication (see also section 4.4).

Remifentanil 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 lyophilized powder. For instructions on reconstitution/dilution of the medicinal product before administration, see section 6.6. For information on storage conditions, see section 6.3.
For manually-controlled infusion Remifentanil can be diluted to concentrations of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 micrograms/ml for paediatric patients aged 1 year and over).
For TCI the recommended dilution of Remifentanil is 20 to 50 micrograms/ml.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to other fentanyl analogues.

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

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/Switch to alternative analgesic treatment
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 agonists 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.

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.

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 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. Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking agent and/or additional hypnotic agents. Muscle rigidity seen during the use of remifentanil as an analgesic may be treated by stopping or decreasing the rate of administration of remifentanil. Resolution of muscle rigidity after discontinuing the infusion of remifentanil occurs within minutes. Alternatively an opioid antagonist may be administered; however this may reverse or attenuate the analgesic effect of remifentanil.

Respiratory depression – 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Remifentanil and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Remifentanil concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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.

Drug abuse

As with other opioids remifentanil may produce dependency.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per ml.

Paediatric population

Neonates and infants

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

4.5 Interaction with other medicinal products and other forms of interactions

Remifentanil is not metabolised by plasmacholinesterase, therefore, interactions with medicinal products metabolized 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 inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (see section 4.2). If doses of concomitantly administered CNS depressant medicinal products are not reduced patients may experience an increased incidence of adverse effects associated with these agents. The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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 in pregnant women. Remifentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Labour and delivery

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

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

4.7 Effects on ability to drive and use machines

Remifentanil has 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
Rare: ≥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 organ class:

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
Not known: cough

Gastrointestinal disorders
Very common:nausea, vomiting
Uncommon: constipation

Skin and subcutaneous tissue disorders

Common: pruritus

General disorders and administration site conditions
Common: post-operative shivering
Uncommon: post-operative pain

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

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 medicinal product administration. Response to discontinuation of the medicinal product 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 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: N01AH06
Remifentanil is a selective μ-opioid agonist with a rapid onset and very short duration of action. The μ-opioid activity of remifentanil is antagonized 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 micrograms/kg.

Paediatric population

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 (N20) 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) (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)	11.8 (4.2)
		Inhalation anaesthesia: sevoflurane (1.0 – 1.5 MAC) and remifentanil (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) + remifentanil (0.5 µg/kg/min)	11 (3.7)
		Inhalation anaesthesia: desflurane (1.3 MAC) and N_2O mixture	9.4 (2.9) Not significant
General or ENT surgery	2-12 (153)	TIVA: remifentanil (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) and N_2O mixture	

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.

Distribution
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 microgram/kg/min increase in i.v. infusion rate, the blood concentration of remifentanil will rise to 2.5 nanogram/ml.

Remifentanil is approximately 70 % bound to plasma proteins.

Biotransformation
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 barrier and breast milk
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 remifentanil concentrations 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.

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

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.

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 pharmacokinetic profile of remifentanil is 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 population
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 2-17 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

Remifentanil, 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 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 formulation, this finding has no clinical relevance for intravenous administration of Remifentanil.

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
There were no long-term carcinogenicity studies performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Hydrochloric acid 37 % (for pH adjustment)
Sodium hydroxide 17 % solution (for pH adjustment)

6.2 Incompatibilities

Remifentanil 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 or Lactated Ringer's and glucose 50 mg/ml (5 %) solution for injection. Remifentanil 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 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 should not be mixed with other therapeutic agents prior to administration.

6.3 Shelf life

2 years
After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 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 has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30 C

Do not refrigerate or freeze.
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

3.5 ml vial of colourless glass (type 1) with bromobutyl rubber stopper and light blue cap.
Pack sizes: 5 vials per pack
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Remifentanil 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 1mg/ml.

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

Following reconstitution, the product should be inspected visually (as far as supported by the vial) for solids, discoloration or damage to the vials. If such changes are detected, the solution has to be discarded. The finished solution is for single use only. Unused solution has to be discarded.

For manually-controlled infusion, Remifentanil should be administered following further dilution to a concentration of 20 to 250 micrograms/ml (50 micrograms/ml is the recommended dilution for adults and 20 to 25 microgram/ml for paediatric patients aged 1 year and over).

For target controlled infusion (TCI), Remifentanil should be administered following further dilution to a concentration of 20 to 50 micrograms/ml.

Dilution should be adjusted to the technical equipment of the infusion system and the expected patient requirements.

The diluted solution is for single use only.

For dilution, one of the following IV fluids listed below should be used:

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

Following dilution, the solution should be inspected visually to ensure that it is clear, colourless and virtually free from solids, and that there is no damage to the vials. If such changes are detected, the solution has to be discarded.

Remifentanil has been shown to be compatible with the following IV 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

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

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/112/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2011
Date of last renewal: 31st January 2015

10 DATE OF REVISION OF THE TEXT

April 2019