Package leaflet: Information for the user

Remifentanil Noridem 1 mg Powder for Concentrate for Solution for Injection or Infusion
Remifentanil Noridem 2 mg Powder for Concentrate for Solution for Injection or Infusion
Remifentanil Noridem 5 mg Powder for Concentrate for Solution for Injection or Infusion

remifentanil

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Remifentanil Noridem is and what it is used for

Remifentanil Noridem contains a medicine called remifentanil. This belongs to a group of medicines known as opioids, which are used for pain relief. Remifentanil Noridem differs from other medicines in this group by its very quick onset and very short duration of action.

Remifentanil Noridem is used:
- To stop you feeling pain before and during an operation.
- To stop you feeling pain while you are under controlled mechanical ventilation in an Intensive Care Unit (for patients 18 years of age and over).

2. What you need to know before you are given Remifentanil Noridem

Do not have Remifentanil Noridem:
- If you are allergic to remifentanil or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to fentanyl analogues (pain-relieving medicines which are similar to fentanyl and which are related to the class of medicines known as opioids).
- As injection in the spinal canal.
- As sole medicine to initiate anaesthesia.

If you are not sure if any of the above apply to you, talk to your doctor, pharmacist or nurse before you are given Remifentanil Noridem.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Remifentanil Noridem if:
- You are allergic to any other opioid medicines, such as morphine or codeine.
- You suffer from impaired lung (you may be more sensitive to breathing difficulties).
- You are over 65 years of age, weak or have decreased blood volume and/or low blood pressure (you are more sensitive to suffer from cardiac disturbances).

If you are not sure if any of the above apply to you, talk to your doctor, pharmacist or nurse, before you are given Remifentanil Noridem.

Tell your doctor before using remifentanil if:
- You or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- You are a smoker.
- You have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

This medicine contains remifentanil which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on Remifentanil Noridem, it is important that you consult your doctor.

Withdrawal reactions including rapid heartbeat, high blood pressure and restlessness have occasionally been reported when treatment with this medicine is stopped suddenly, particularly when treatment has lasted more than 3 days (see also section 4. Possible side effects). If you experience these symptoms, your doctor may re-introduce the medicine and gradually reduce the dose.

Other medicines and Remifentanil Noridem
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you can obtain without a prescription.

In particular tell your doctor or pharmacist if you are taking:
- Medicines for your heart or blood pressure, such as beta-blockers or calcium channel blockers.
- Medicines for the treatment of depression such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Monoamine Oxidase Inhibitors (MAOIs). It is not recommended to use these medicines at the same time as Remifentanil Noridem as they may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Concomitant use of Remifentanil Noridem and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening.
Because of this, concomitant use should only be considered when other treatment options are not possible. The concomitant use of opioids and drugs used to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and may be life-threatening.

However, if your doctor does prescribe Remifentanil Noridem together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Remifentanil Noridem with alcohol
After receiving Remifentanil Noridem, you should not drink alcohol until you have fully recovered.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Your doctor will weigh up the benefit to you against the risk to your baby of receiving this medicine while you're pregnant.

If you are given this medicine during labour or close to childbirth, it can affect your baby's breathing. You and your baby will be monitored for signs of excessive sleepiness and difficulty breathing.

You should stop breast-feeding your baby for 24 hours after receiving this medicine. If you express any breast milk during this time, discard the milk and don't give it to your baby.

Driving and using machines
If you are only staying in hospital for the day, your doctor will tell you how long to wait before leaving the hospital or driving a car. It can be dangerous to drive too soon after having an operation.

3. How Remifentanil Noridem is given

You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so.

Remifentanil Noridem can be given:
- As a single injection into your vein
- As a continuous infusion into your vein. This is where the drug is slowly given to you over a longer period of time.

The way you are given the drug and the dose you receive will depend on:
- The operation or treatment in the Intensive Care Unit you have
- How much pain you will be in

The dose varies from one patient to another. There is no dosing adjustment needed for patients with kidney and liver problems.

If you are given too much
The effects of Remifentanil Noridem are carefully monitored throughout your operation and in intensive care, and appropriate action will be taken promptly if you receive too much.

After your operation
Tell your doctor or nurse if you are in pain. If you are in pain after your procedure, they will be able to give you other painkillers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions including anaphylaxis: These are rare (may affect up to 1 in 1 000 people) in people taking Remifentanil Noridem. Signs include:
- Raised and itchy rash (hives).
- Swelling of the face or mouth (angioedema) causing difficulty in breathing.
- Collapse.

Severe allergic reactions can progress to life-threatening anaphylactic shock;
Frequency not known (cannot be estimated from the available data) which include worsening of allergic signs, severe drop in blood pressure, heart beats quickly and/or fainting.

If you notice any of these symptoms contact a doctor urgently.

Very common side effects
These may affect **more than 1 in 10 people:**
- Muscle stiffness *(muscle rigidity)*.
- Low blood pressure *(hypotension)*.
- Feeling sick *(nausea)* or being sick *(vomiting)*.

Common side effects
These may affect **up to 1 in 10 people:**
- Slow heartbeat *(bradycardia)*.
- Shallow breathing *(respiratory depression)*.
- Temporarily stopping breathing *(apnoea)*.
- Itching.
- Cough.

Uncommon side effects
These may affect **up to 1 in 100 people:**
- Oxygen deficiency *(hypoxia)*.
- Constipation.

Rare side effects
These may affect **up to 1 in 1 000 people:**
- Slow heart beat *(bradycardia)* followed by absence of heartbeat (*asystole/cardiac arrest*) in patients receiving Remifentanil Noridem with one or more anaesthetic medicines.

Other side effects
Other side effects have occurred in a very small number of people but their exact frequency is unknown:
- Physical need for remifentanil (drug dependency) or the need for increasing doses over time to get the same effect (drug tolerance).
- Fits (seizures).
- A type of irregular heartbeat (atrioventricular block).
- Irregular heartbeat (arrhythmia).
- Withdrawal syndrome (may manifest by the occurrence of the following side effects: increased heart rate, high blood pressure, feeling restless or agitated, nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating).

Side effects that you can get after your operation

Common side effects (may affect up to 1 in 10 people)
- Shivering.
- High blood pressure *(hypertension)*.

Uncommon side effects (may affect up to 1 in 100 people)
- Aches.

Rare side effects (may affect up to 1 in 1 000 people)
- Feeling very calm or drowsy.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Remifentanil Noridem

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and carton after “EXP”. The expiry date refers to the last day of that month.

Do not use the reconstituted product unless it is clear, colourless and practically free from particulate material.

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

After reconstitution/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/dilution has taken place in controlled and validated aseptic conditions.

Any unused solution should not be disposed of via wastewater or household waste. Your doctor or nurse will throw away any medicine that is no longer required. This will help protect the environment.

6. Contents of the pack and other information

What Remifentanil Noridem contains
- The active substance is remifentanil. Each vial contains 1 mg, 2 mg or 5 mg of remifentanil (as hydrochloride).
- The other ingredients are glycine and hydrochloric acid *(for pH adjustment)*.

What Remifentanil Noridem looks like and contents of the pack
Remifentanil Noridem is a white to off-white powder. The powder will be mixed with an appropriate fluid before being injected. When mixed to form a solution, Remifentanil Noridem is clear and colourless.

Remifentanil Noridem 1 mg Powder for Concentrate for Solution for Injection or Infusion is available in a glass vial with bromobutyl rubber stopper and aluminium seal with a light blue plastic flip-off cap.
Remifentanil Noridem 2 mg Powder for Concentrate for Solution for Injection or Infusion is available in a glass vial with bromobutyl rubber stopper and aluminium seal with a blue plastic flip-off cap.
Remifentanil Noridem 5 mg Powder for Concentrate for Solution for Injection or Infusion is available in a glass vial with bromobutyl rubber stopper and aluminium seal with a dark blue plastic flip-off cap.

Each strength of Remifentanil Noridem is supplied in cartons containing 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Noridem Enterprises Ltd., Evagorou & Makariou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus.
Manufacturer: DEMO S.A., 21st km National Road Athens-Lamia, 14568 Krioneri, Attiki, Greece.

This medicine is authorised in the Member States of the European Economic Area under the following names:

Ireland:	Remifentanil Noridem 1mg, 2mg & 5mg Powder for Concentrate for Solution for Injection or Infusion
Austria:	Remifentanil Noridem 1 mg, 2mg & 5mg Pulver für ein Konzentrat zur Herstellung einer Injektions- oder Infusionslösung
Greece:	Remifentanil/Noridem Κόνις για πυκνό σκεύασμα για Παρασκευή Διαλύματος προς Ένεση ή Έγχυση, 1mg/vial, 2mg/vial & 5mg/vial
Spain:	Remifentanilo Noridem 1 mg, 2mg & 5mg polvo para concentrado para solución inyectable y para perfusión EFG

This leaflet was last revised in 03/2025.

The following information is intended for medical or healthcare professionals only:

For detailed information please refer to the Summary of Product Characteristics of Remifentanil Noridem.

Posology and method of administration

Remifentanil Noridem 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 Noridem must be administered by a calibrated infusion device into a fast flowing IV line or via a dedicated IV line. This infusion line should be connected at, or close to, the venous cannula and primed, to minimise the potential dead space (see *Special precautions for disposal and other handling* for additional information and section 6.6 of the SmPC for tables with examples of infusion rates by body weight to help titrate Remifentanil Noridem to the patient's anaesthetic needs).

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

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Remifentanil Noridem after use (see *Special warnings and precautions for use*). Remifentanil Noridem is for intravenous use only and must not be administered by epidural or intrathecal injection (see *Contraindications*).

Dilution
Remifentanil Noridem may be further diluted after reconstitution. For instructions on dilution of the medicinal product before administration, see *Special precautions for disposal and other handling*.

For manually-controlled infusion Remifentanil Noridem 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 Noridem is 20 to 50 micrograms/mL.

General Anaesthesia

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

Adults

Administration by Manually-Controlled Infusion

Table 1 summarises the starting injection/infusion rates and dose range:

Table 1. Dosing Guidelines for Adults

INDICATION	BOLUS INJECTION (micrograms/kg)	CONTINUOUS INFUSION (micrograms/kg/min)	
		Starting Rate	Range

Induction of anaesthesia	1 (give over not less than 30 seconds)	0.5 to 1	_
Maintenance of anaesthesia in ventilated patients			
• 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 micrograms/kg/min)	0.5 to 1	0.25	0.05 to 2

When given by slow bolus injection Remifentanil Noridem 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 such as hypotension and bradycardia (see this section *Concomitant medication*).

No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in Table 1 with remifentanil.

Induction of anaesthesia: Remifentanil Noridem should be administered with a standard dose of hypnotic agent, such as propofol, thiopental, or isoflurane, for the induction of anaesthesia. Remifentanil Noridem can be administered at an infusion rate of 0.5 to 1 micrograms/kg/min, with or without an initial slow bolus injection of 1 microgram/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 Noridem, then a bolus injection is not necessary.

Maintenance of anaesthesia in ventilated patients: After endotracheal intubation, the infusion rate of Remifentanil Noridem should be decreased, according to anaesthetic technique, as indicated in Table 1. Due to the fast onset and short duration of action of Remifentanil Noridem, the rate of administration during anaesthesia can be titrated upward in 25% to 100% increments or downward in 25% to 50% decrements, every 2 to 5 minutes to attain the desired level of μ-opioid response. In response to light anaesthesia, supplemental slow bolus injections may be administered every 2 to 5 minutes.

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

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

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

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

Guidelines for discontinuation/continuation into the immediate post-operative period: Due to the very rapid offset of action of Remifentanil Noridem 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 Noridem. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care.

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

Guidance on use in mechanically ventilated intensive care patients is provided in this section *Use in intensive care*.

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

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

Administration by Target-Controlled Infusion

Induction and maintenance of anaesthesia in ventilated patients: Remifentanil Noridem 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, in this section *General anaesthesia*).

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 nanograms/mL. Remifentanil Noridem should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 nanograms/mL may be required.

At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see Table 1 and this section *Concomitant medication*).

For information on blood remifentanil concentrations achieved with manually-controlled infusion see section 6.6 of the SmPC, Table 11.

As there are insufficient data, the administration of Remifentanil Noridem 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 nanograms/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see this section *Administration by manually-controlled infusion – Guidelines for discontinuation*).

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

Paediatric patients (1 to 12 years of age)

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

Remifentanil Noridem TCI has not been studied in paediatric patients and therefore administration of Remifentanil Noridem by TCI is not recommended in these patients. The following doses of Remifentanil Noridem are recommended for maintenance of anaesthesia:

Table 2. Dosing Guidelines for Paediatric Patients (1 to 12 years of age)

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

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

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

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

Guidelines for patient management in the immediate post-operative period/ Establishment of alternative analgesia prior to discontinuation of Remifentanil Noridem: Due to the very rapid offset of action of Remifentanil Noridem, 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 Noridem. 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 *Special warnings and precautions for use*).

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 of the SmPC). 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 of the SmPC). 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 of the SmPC). However, there are insufficient clinical data to make dosage recommendations.

Cardiac anaesthesia

Administration by Manually-Controlled Infusion

Table 3. Dosing Guidelines for Cardiac Anaesthesia

INDICATION	BOLUS INJECTION (micrograms/kg)	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 period of anaesthesia: After administration of hypnotic to achieve loss of consciousness, Remifentanil Noridem should be administered at an initial infusion rate of 1 microgram/kg/min. The use of bolus injections of Remifentanil Noridem 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 Noridem should be titrated according to patient need. Supplemental slow bolus doses may also be given as required. High-risk cardiac patients, such as those with poor ventricular function or undergoing valve surgery, should be administered a maximum bolus dose of 0.5 micrograms/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see section 5.2 of the SmPC).

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

Guidelines for post-operative patient management

Continuation of Remifentanil Noridem post-operatively to provide analgesia prior to weaning for extubation: It is recommended that the infusion of Remifentanil Noridem 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 Noridem infusion rate adjusted to meet the individual patient's requirements (see this section *Use in intensive care*, for further information on management of intensive care patients).

Establishment of alternative analgesia prior to discontinuation of Remifentanil Noridem: Due to the very rapid offset of action of Remifentanil Noridem, no residual opioid activity will be present within 5 to 10 minutes after discontinuation. Prior to discontinuation of Remifentanil Noridem, 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 Noridem: Due to the very rapid offset of action of Remifentanil Noridem, hypertension, shivering and aches have been reported in cardiac patients immediately following discontinuation of Remifentanil Noridem (see section 4.8 of the SmPC). To minimise the risk of these occurring, adequate alternative analgesia must be established (as described above), before the Remifentanil Noridem 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 Noridem 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: Remifentanil Noridem 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 3). 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 used in clinical studies. At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid an increase of haemodynamic effects such as hypotension and bradycardia (see Table 3 and this section *Concomitant medication*).

For information on blood remifentanil concentrations achieved with manually-controlled infusion see section 6.6 of the SmPC, Table 11.

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 nanograms/mL. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see this section *Administration by manually-controlled infusion – Guidelines for discontinuation*).

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

Paediatric patients (1 to 12 years of age)

There are insufficient data to make a dosage recommendation for use during cardiac surgery.

Use in intensive care

Adults

Remifentanil Noridem can be used for the provision of analgesia in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.

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

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

In adults, it is recommended that Remifentanil Noridem 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 regularly assessed and the Remifentanil Noridem infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min (12 micrograms/kg/h) is reached and sedation is required, it is recommended that dosing with an appropriate sedative agent is initiated (see below). The dose of sedative agent should be titrated to obtain the desired level of sedation. Further increases to the Remifentanil Noridem infusion rate in increments of 0.025 micrograms/kg/min (1.5 micrograms/kg/h) may be made if additional analgesia is required.

Table 4 summarises the starting infusion rates and typical dose range for provision of analgesia in individual patients:

Table 4. Dosing Guidelines for use of Remifentanil Noridem 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 (0.38) to 0.74 (44.6)

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

The use of Remifentanil Noridem will reduce the dosage requirement of any concomitant sedative agents. Typical starting doses for sedative agents, if required, are given in Table 5.

Table 5. Recommended starting dose of sedative agents, if required:

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

To allow separate titration of the respective agents, sedative agents should not be prepared as one mixture in the same infusion bag.

Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the existing Remifentanil Noridem 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 Noridem infusion rate of at least 0.1 micrograms/kg/min (6 micrograms/kg/h) should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25% to 50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min (15 micrograms/kg/h), maximum 0.74 micrograms/kg/min (45 micrograms/kg/h), has been administered for provision of additional analgesia during stimulating procedures.

Establishment of alternative analgesia prior to discontinuation of Remifentanil Noridem: Due to the very rapid offset of action of Remifentanil Noridem, no residual opioid activity will be present within 5 to 10 minutes after discontinuation regardless of the duration of infusion. Following administration of Remifentanil Noridem, the possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit (*see section 4.4 Special warnings and precautions for use* of the SmPC). Therefore, prior to discontinuation of Remifentanil Noridem, patients must be given alternative analgesic and sedative agents to prevent hyperalgesia and associated haemodynamic changes. These agents must be given at a sufficient time in advance to allow the therapeutic effects of these agents to become established. The range of options for analgesia includes long acting oral, intravenous, or

regional analgesics controlled by the nurse or the patient. These techniques should always be titrated to individual patient needs as the infusion of Remifentanil Noridem is reduced. It is recommended that the choice of agent(s), the dose, and the time of administration are planned prior to discontinuation of Remifentanil Noridem.

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

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

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

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

Paediatric intensive care patients

There are no data available on use in paediatric patients.

Renally-impaired intensive care patients

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

Special patient populations

Elderly (over 65 years of age)

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

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

Intensive Care: No initial dose reduction is required (see this section *Use in intensive care*).

Obese patients

For manually-controlled infusion it is recommended that for obese patients the dosage of Remifentanil Noridem 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.

Renal impairment

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

Hepatic impairment

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

Neurosurgery

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

ASA III/IV patients

General anaesthesia: As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised in the administration of Remifentanil Noridem in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended. In paediatric patients, there are insufficient data to make a dosage recommendation.

For TCI, a lower initial target of 1.5 to 4 nanograms/mL should be used in ASA III or IV patients and subsequently titrated to response.

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

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

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

Shelf life

After reconstitution/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/dilution has taken place in controlled and validated aseptic conditions**.**

Special precautions for disposal and other handling

Remifentanil Noridem should be prepared for intravenous use by adding, as appropriate 1, 2, or 5 mL of diluent to give a reconstituted solution with a concentration of 1 mg/mL remifentanil. The reconstituted solution is clear, colourless, and practically free from particulate material. After reconstitution, visually inspect the product (where the container permits) for particulate material, discolouration or damage of container. Discard any solution where such defects are observed. Reconstituted product is for single use only. Any unused material should be discarded.

Remifentanil Noridem should not be administered by manually-controlled infusion without further dilution 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).

Remifentanil Noridem should not be administered by TCI without further dilution (20 to 50 micrograms/mL is the recommended dilution for TCI).

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

One of the following IV fluids listed below should be used for dilution:

Water for Injections

Glucose 5% solution for injection

Glucose 5% and Sodium Chloride 0.9% solution for injection

Sodium Chloride 0.9% solution for injection

Sodium Chloride 0.45% solution for injection

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

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

Lactated Ringer's solution for injection

Lactated Ringer's and Glucose 5% solution for injection

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

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