Package leaflet: Information for the patient

Ultiva 1 mg powder for concentrate for solution for infusion
Ultiva 2 mg powder for concentrate for solution for infusion
Ultiva 5 mg powder for concentrate for solution for 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 Ultiva is and what it is used for

Ultiva contains a medicine called remifentanil. This belongs to a group of medicines known as opioids.

It is used:
- to help put you to sleep **before** an operation in combination with other medicines
- to keep you asleep and stop you feeling pain **during** an operation in combination with other medicines, while your breathing and heart are monitored and supported
- alone or in combination with other medicines, to make you feel sleepy and stop you feeling pain while you receive treatment in an Intensive Care Unit (ICU).

2. What you need to know before you are given Ultiva

Do not have Ultiva if:
- you are allergic (hypersensitive) to remifentanil or any of the other ingredients of this medicine (listed in Section 6)
- you are allergic (hypersensitive) to fentanyl analogues (pain relieving medicines which are similar to fentanyl and which are related to the class of medicines known as opioids).

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

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Ultiva if:
- you are allergic (hypersensitive) to any other opioid medicines, such as morphine or codeine
- you are over 65 years of age

- you are obese
- you have severely impaired liver function
- you suffer from a severe systemic disease that limits your activity and may be a threat to your life. Your doctor will advise if this medicine is suitable for you
- you are dehydrated or have lost a lot of blood
- you have been feeling unwell
- you have been told that you have a slow or irregular heartbeat or low blood pressure
- you have problems with your lungs (respiratory dysfunction).

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

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 Ultiva, 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.

Mechanically-ventilated ICU patients
Use of this medicine in patients whose breathing is being artificially assisted in an ICU is for those patients over 18 years only and should be used for a maximum of 3 days.

Children aged 1 to 12 years
For children aged 1 to 12 years, this medicine is used to keep them asleep and stop them feeling pain **during** an operation but should not be used to help put them asleep **before** an operation.

Children under 1 year
This medicine is not recommended for use in children less than 1 year.

Drug tolerance
Following use of this medicine, there is a possibility that your response to the drug may decrease such that you may become sensitive to pain at the prescribed dose. This is more likely to happen when Ultiva is used over a long period of time.

Drug dependence

This medicine may produce dependency, making you feel that you need it to function normally.

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

Other medicines and Ultiva
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes herbal medicines. This is because Ultiva can work with other medicines to cause side effects.

In particular tell your doctor or pharmacist if you are taking:
- medicines for your heart or blood pressure, such as beta-blockers (these include atenolol, metoprolol and bisoprolol) or calcium channel blockers (these include amlodipine, diltiazem and nifedipine).
- 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 Ultiva as they may increase the risk of serotonin syndrome, a potentially life-threatening condition.

This medicine reduces the amount of other drugs which will be needed to put you to sleep, relax you before an operation and/or stop you feeling pain (hypnotics). This is to reduce the risk of side effects from these drugs.

Concomitant use of Ultiva 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 Ultiva 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.

Ultiva with food and alcohol
You should avoid alcoholic drink after having this medicine.

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.

The safety of this medicine has not fully been established in pregnant women. This medicine should only be given to pregnant women if the doctor considers that the benefit for the mother exceeds any possible risk to the foetus.

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.

It is advised that you don't breast-feed your baby for 24 hours after getting this medicine as the active ingredient (remifentanil) may be excreted in the breast milk.

Driving and using machines
Do not drive or operate machinery after having this medicine. Your doctor will tell you when it is safe to do so again. It is recommended that you arrange for someone to accompany you home from the hospital.

Ultiva contains Sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.

3. How Ultiva is given

How your injection 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.

This medicine is for injection into the vein only. Ultiva **will not** be used on its own to put you asleep before an operation. It **will** be used in combination with other medicines.

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

The dose you receive will depend on:
- the operation you have
- how much pain you will be in
- how sleepy the medical staff want you to be in the ICU.

The dose varies from one patient to another and will be decided by your doctor.

Mechanically-ventilated ICU patients
Use of this medicine in patients whose breathing is being artificially assisted in an ICU is for those patients over 18 years only and should be used for a maximum of 3 days.

Children aged 1 to 12 years
For children aged 1 to 12 years, this medicine is used to keep them asleep and stop them feeling pain **during** an operation but should not be used to help put them asleep **before** an operation.

Children under 1 year
This medicine is not recommended for use in children less than 1 year.

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. The following side effects may happen with this medicine.

Some people can be allergic to Ultiva. **You must tell your doctor or nurse immediately if you have**:

Rare (may affect up to 1 in 1,000 people)
- sudden wheeziness and chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- a lumpy skin rash or 'hives' anywhere on the body
- a collapse.

Tell your doctor **as soon as possible** if you notice any of the following:

Very common (may affect more than 1 in 10 people)
- muscle stiffness.

Common (may affect up to 1 in 10 people)
- difficulty breathing.

Your doctor or nurse will then adjust your dose accordingly.

Other side effects that can happen when you wake up after having an anaesthetic include:

Very common (may affect more than 1 in 10 people):
- feeling sick (nausea)
- being sick (vomiting)
- low blood pressure (hypotension).

Common (may affect up to 1 in 10 people):
- increases in blood pressure
- itching
- shivering
- a very slow heartbeat.
- cough

Uncommon (may affect up to 1 in 100 people):
- rapid breathing, hot and cold flushes, poor coordination, headache, a tingling feeling, visual impairment (Hypoxia, an insufficient oxygen supply to the body)
- constipation
- aches.

Rare (may affect up to 1 in 1,000 people):
- feeling very calm or drowsy (sedation)

- asystole (no heartbeat) or cardiac arrest
- a severe, whole-body allergic reaction (anaphylaxis).

Not known (frequency cannot be estimated from the available data):
- drug dependence (needing the medicine to function normally)
- convulsions (uncontrolled shaking of the body)
- dizziness, fainting, chest pain and breathlessness (atrioventricular block, a delay in the electrical impulse reaching the lower chambers of the heart)
- drug tolerance (response to the drug may decrease such that you may become sensitive to pain at the prescribed dose)
- 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).

Possible withdrawal symptoms

If you experience any of these side effects, or any other side effects whilst stopping this medicine, please speak to your doctor.

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:

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ultiva

- Keep this medicine out of the sight and reach of children.
- Do not use Ultiva 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 store above 25°C.
- When Ultiva is made up it should be used straight away. 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.
- Store in the original package with this leaflet.

6. Contents of the pack and other information

What Ultiva contains

The active substance is remifentanil hydrochloride.

- Each vial of Ultiva 1 mg powder for concentrate for solution for infusion contains 1 mg remifentanil (as remifentanil hydrochloride).
- Each vial of Ultiva 2 mg powder for concentrate for solution for infusion contains 2 mg remifentanil (as remifentanil hydrochloride).
- Each vial of Ultiva 5 mg powder for concentrate for solution for infusion contains 5 mg remifentanil (as remifentanil hydrochloride).

The other ingredients are glycine, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment if needed).

What Ultiva looks like and contents of the pack

Ultiva is available in the following strengths:

- Ultiva 1 mg powder for concentrate for solution for infusion is a white to off-white, lyophilised powder, in 3 ml glass vials.
- Ultiva 2 mg powder for concentrate for solution for infusion is a white to off-white, lyophilised powder, in 5 ml glass vials.
- Ultiva 5 mg powder for concentrate for solution for infusion is a white to off-white, lyophilised powder, in 10 ml glass vials.

The powder will be mixed with an appropriate fluid before being injected. When mixed to form a solution, Ultiva is clear and colourless.
Each strength of Ultiva is supplied in cartons containing 5 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland.
Tel: +353 1 6 308 400 (Ireland)
Tel: +356 21 497 982 (Malta)

Manufacturer:
GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana 90, 43056 San Polo di Torrile, Parma, Italy.
or
Aspen Pharma Ireland Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland
or
Aspen Bad Oldesloe GmbH
Industriestrasse 32-36
23843 Bad Oldesloe
Germany

This leaflet was last revised in

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THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY

(Please refer to the Summary of Product Characteristics (SPC) for further information)

Ultiva 1 mg powder for concentrate for solution for infusion
Ultiva 2 mg powder for concentrate for solution for infusion
Ultiva 5 mg powder for concentrate for solution for infusion
remifentanil

Pharmaceutical forms

Ultiva 1 mg powder for concentrate for solution for infusion
Ultiva 2 mg powder for concentrate for solution for infusion
Ultiva 5 mg powder for concentrate for solution for infusion

Posology and method of administration

Ultiva shall be administered in hospitals 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 Ultiva must be administered by a calibrated infusion device into a fast flowing intravenous (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.

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Ultiva after use.

Ultiva is for IV use only and must not be administered by epidural or intrathecal injection.

Dilution
Ultiva may be further diluted after reconstitution.

For manually-controlled infusion Ultiva 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).

GENERAL ANAESTHESIA
The administration of Ultiva must be individualised based on the patient's response.

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

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 0.5MAC)	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 at induction Ultiva shall be administered over not less than 30 seconds.

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

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

Induction of anaesthesia: Ultiva should be administered with a reduced dose of hypnotic agent, such as propofol, thiopentone, or isoflurane, for the induction of anaesthesia. Ultiva 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 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 Ultiva, then a bolus injection is not necessary.

Maintenance of anaesthesia in ventilated patients: After endotracheal intubation, the infusion rate of Ultiva should be decreased, according to anaesthetic technique, as indicated in the above table. Due to the fast onset and short duration of action of Ultiva, the rate of administration during anaesthesia can be titrated upward in 25% to 100% increments or downward in 25% to 50% decrements, every 2 to 5 minutes to attain the desired level of mu-opioid response. In response to light anaesthesia, supplemental slow bolus injections, over not less than 30 seconds may be administered every 2 to 5 minutes.

Concomitant medication: Ultiva decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia.

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

Guidelines for discontinuation: Due to the very rapid offset of action of Ultiva no residual opioid activity will be present within 5 to 10 minutes after discontinuation. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to discontinuation of Ultiva. Sufficient time must be allowed to reach the maximum effect of the longer acting analgesic. The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care.

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

Paediatric patients (1 to 12 years of age)
Co-administration of Ultiva and an IV anaesthetic agent for induction of anaesthesia has not been studied in detail and is therefore not recommended.

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

Dosing guidelines for maintenance of anaesthesia in 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-administration with nitrous oxide/oxygen in a ratio of 2:1

When given by bolus injection Ultiva should be administered **over not less than 30 seconds**. Surgery should not commence until at least 5 minutes after the start of the Ultiva infusion, if a simultaneous bolus dose has not been given. For sole administration of nitrous oxide (70%) with Ultiva, typical maintenance infusion rates should be between 0.4 and 3 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, Ultiva 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 Ultiva.

Guidelines for patient management in the immediate post-operative period

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

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

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

CARDIAC ANAESTHESIA

Adults

Dosing guidelines for cardiac anaesthesia

INDICATION	*BOLUS INJECTION* (micrograms/kg)	*CONTINUOUS INFUSION* (micrograms/kg/min)	
		Starting Rate	*Typical Infusion Rates*
Induction of anaesthesia	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, Ultiva should be administered at an initial infusion rate of 1 micrograms/kg/min. The use of bolus injections of Ultiva 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 Ultiva 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 should be administered a maximum bolus dose of 0.5 micrograms/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass.

Concomitant medication:
At the doses recommended above, Ultiva 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 Ultiva.

Continuation of Ultiva post-operatively to provide analgesia prior to extubation:
It is recommended that the infusion of Ultiva 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 Ultiva infusion rate adjusted to meet the individual patient's requirements.

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

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

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

USE IN INTENSIVE CARE
Ultiva can be used for the provision of analgesia in mechanically ventilated intensive care patients of 18 years of age and over. Sedative agents should be used as appropriate.

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

In adults, it is recommended that Ultiva is initiated at an infusion rate of 0.1 microgram/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 Ultiva 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 Ultiva 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 Ultiva 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 Ultiva are not recommended in the intensive care setting.

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

Recommended starting dose of sedative agents, if required:

Sedative Agents	*Bolus (mg/kg)*	*Infusion (mg/kg/h)*
Propofol	Up to 0. 5	0. 5
Midazolam	Up to 0.03	0.03

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

Additional analgesia for ventilated patients undergoing stimulating procedures:
An increase in the existing Ultiva infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that an Ultiva 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 anaesthesia during stimulating procedures.

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

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

Guidelines for extubation and discontinuation of Ultiva:
In order to ensure a smooth emergence from an Ultiva-based regimen it is recommended that the infusion rate of Ultiva is titrated in stages to 0.1 microgram/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 Ultiva infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

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

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

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.

SPECIAL PATIENT POPULATIONS

Elderly (over 65 years of age)
General Anaesthesia: The initial starting dose of Ultiva 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 Ultiva has been seen in this patient population. This dose adjustment applies to use in all phases of anaesthesia.

Cardiac Anaesthesia: No initial dose reduction is required.

Intensive Care: No initial dose reduction is required.

Obese patients
It is recommended that for obese patients the dosage of Ultiva 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.

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

Neurosurgery
There is only limited clinical experience in patients undergoing neurosurgery and insufficient information to recommend a dose.

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 Ultiva 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.

Cardiac Anaesthesia: No initial dose reduction is required.

Overdose
Symptoms and signs
As with all potent opioid analgesics, overdose would be manifested by an extension of the pharmacologically predictable actions of remifentanil. Due to the very short duration of action of Ultiva, the potential for deleterious effects due to overdose are limited to the immediate time period following drug administration. Response to discontinuation of the drug is rapid, with return to baseline within 10 minutes.

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

IV 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 Ultiva is unlikely to exceed the duration of action of the opioid antagonist.

Shelf life and special precautions for storage

Unopened:
Ultiva 1 mg - 18 months
Ultiva 2 mg - 2 years
Ultiva 5 mg - 3 years

Do not store above 25°C.

Following reconstitution/dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (25^{o}C). Ultiva should not be administered without further dilution. From a microbiological point of view, both the reconstituted product and the diluted product should be used immediately, following preparation. 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^{o}C, unless reconstitution/dilution has taken

place in controlled and validated aseptic conditions. Any unused solution remaining after this time should be discarded.

Instructions for use and handling

Ultiva should be prepared for IV use by adding, as appropriate 1, 2 or 5 ml of diluent to give a reconstituted solution with a concentration of approximately 1 mg/ml remifentanil. The reconstituted solution is clear, colourless, and practically free from particulate material. After reconstitution, Ultiva should not be administered 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) with one of the following IV fluids listed below:

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

- Sterilised Water for Injections
- 5% Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Injection

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

- Lactated Ringer's Injection
- Lactated Ringer's and 5% Dextrose Injection

Ultiva 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.

Please refer to the SPC for guidelines as to the infusion rates of Ultiva.

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