GlaxoSmithKline 10000000049113

For the Medical Profession

Ultiva™ for Injection

remifentanil hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultiva is a sterile, endotoxin-free, preservative-free, white to off-white, lyophilized powder, to be reconstituted before use.
When reconstituted as directed, solutions of Ultiva are clear and colourless and contain 1mg/ml of remifentanil base as remifentanil hydrochloride.
Ultiva for injection is available as glass vials containing 1mg, 2mg or 5mg of remifentanil base.

PHARMACEUTICAL FORM

Lyophilized powder for reconstitution for intravenous administration.

CLINICAL PARTICULARS

Therapeutic indications

Ultiva is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia under close supervision.
Ultiva is indicated for provision of analgesia in mechanically ventilated intensive care patients.

Posology and method of administration

Ultiva 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.
These requirements especially apply to use during the post-operative period.
Continuous infusions of Ultiva 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.
Ultiva is for intravenous use only and must not be administered by epidural or intrathecal injection, as glycine is present in the formulation.
There is a potential for the development of tolerance during the administration of μ-opioid agonists.
Ultiva 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) (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 Ultiva after use.

General Anaesthesia - Adults

Administration by Manually-Controlled Infusion

The administration of Ultiva must be individualised based on the patient's response. Specific dosing guidelines for patients undergoing cardiac surgery are provided in the section headed 'Cardiac Surgery' below.
The following table summarises the starting infusion rates and dose range:

DOSING GUIDELINES FOR ADULTS

INDICATION	BOLUS INJECTION (microgram/kg)	CONTINUOUS INFUSION (microgram/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 microgram/kg/min)	0.5 to 1	0.25	0.05 to 2

When given by slow bolus injection at induction Ultiva 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 excessive depth of anaesthesia (see *Concomitant medication* below).
No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil.
Induction of anaesthesia: Ultiva should be administered with a standard 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 microgram/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 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 'Dosing Guidelines for Adults' 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 μ-opioid response. In response to light anaesthesia, supplemental slow bolus injections may be administered every 2 to 5 minutes.
Spontaneous ventilation anaesthesia: In spontaneous ventilation anaesthesia respiratory depression is likely to occur. Special care is needed to adjust the dose to the patient and ventilatory support may be required. The recommended starting infusion rate for induction and maintenance of anaesthesia is 0.04 microgram/kg/min with titration to effect. A range of infusion rates from 0.025 to 0.1 microgram/kg/min has been studied. Bolus doses are not recommended.
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 remifentanil.
Guidelines for discontinuation/continuation into the immediate post-operative period: 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.
In the event that longer acting analgesia has not been established prior to the end of surgery, Ultiva may need to be continued to maintain analgesia during the immediate post-operative period until longer acting analgesia has reached its maximum effect.
In patients who are breathing spontaneously, the infusion rate of Ultiva should initially be decreased to a rate of 0.1 μg/kg/min. The infusion rate may then be increased or decreased by not greater than 0.025 μg/kg/min every five minutes, to balance the patient's level of analgesia and respiratory rate. Ultiva 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 Ultiva 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: Ultiva 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 'Dosing Guidelines for Adults' table under 'Administration by 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. Ultiva should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 ng/ml may be required.
At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia (see 'Dosing Guidelines for Adults table' and '*Concomitant Medication*' under 'Administration by Manually-Controlled Infusion')
There are insufficient data to make recommendations on the use of TCI for spontaneous ventilation anaesthesia.
Guidelines for discontinuation/ continuation into the immediate post-operative period: At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see '*Guidelines for discontinuation*' under 'Administration by Manually-Controlled Infusion')
As there are insufficient data, the administration of Ultiva by TCI for the management of post-operative analgesia is not recommended.

General Anaesthesia - Paediatric patients (1 to 12 years of age)

Co-administration of Ultiva with induction agents has not been studied.
Ultiva TCI has not been studied in paediatric patients and therefore administration of Ultiva by TCI is not recommended in these patients.
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 μg/kg/min, and although not specifically studied, adult data suggest that 0.4 μg/kg/min is an appropriate starting rate.
Paediatric patients should be monitored and the dose titrated to the depth of analgesia appropriate for the surgical procedure.
Maintenance of anaesthesia
The following doses of Ultiva are recommended for maintenance of anaesthesia:

DOSING GUIDELINES FOR PAEDIATRIC PATIENTS (1 to 12 YEARS OF AGE)

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

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

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 excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil (see Adults - *Concomitant medication*).
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 (see Special warnings and precautions for use).

Neonates/infants (aged less than 1 year):
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. However, there are insufficient clinical data to make dosage recommendations for this age group.

Elderly (over 65 years of age):
General anaesthesia: Caution should be exercised in the administration of Ultiva in this population. The initial starting dose of Ultiva administered to patients over 65 should be half the recommended adult dose and then titrated to individual patient need as an increased sensitivity to the pharmaco-dynamic 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 Ultiva, when administering Ultiva by TCI in this population the initial target concentration should be 1.5 to 4 ng/ml with subsequent titration to response.
Cardiac anaesthesia: No initial dose reduction is required (see Cardiac Surgery).
Intensive care: No initial dose reduction is required (see Intensive Care).

Cardiac Surgery

Administration by Manually-Controlled Infusion

DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

INDICATION	BOLUS INJECTION (microgram/kg)	CONTINUOUS INFUSION (microgram/kg/min)	
		Starting Rate	Range
Intubation	Not recommended	1	–
Maintenance of anaesthesia in ventilated patients			
• Isoflurane (starting dose 0.4MAC)	0.5 to 1	1	0.003 to 4
• Propofol (starting dose 50 microgram/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 microgram/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 can 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 microgram/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass.
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 to avoid excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics with remifentanil (see above under General Anaesthesia - Adults - *Concomitant medication*).

Guidelines for post-operative patient management

Continuation of Ultiva post-operatively to provide analgesia prior to weaning for extubation: It is recommended that the infusion of Ultiva 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 (see Intensive Care, below, for further information on management of intensive care patients).
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 be 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 Undesirable effects). 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.

Administration by Target-Controlled Infusion

Induction and maintenance of anaesthesia: Ultiva 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 'Dosing Guidelines for Cardiac Anaesthesia' table under 'Administration by Manually-Controlled Infusion'). In association with these agents, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 ng/ml have been used in clinical studies. At the doses recommended above, remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia. Therefore, isoflurane and propofol should be administered as recommended above to avoid excessive depth of anaesthesia (see 'Dosing Guidelines for Cardiac Anaesthesia' table and '*Concomitant medication*' under 'Administration by Manually-Controlled Infusion').
Guidelines for discontinuation/continuation into the immediate post-operative period: At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration

is likely to return at calculated remifentanil concentrations in the region of 1 to 2 ng/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics (see '*Guidelines for discontinuation*' under 'Administration by Manually-Controlled Infusion').
As there are insufficient data, the administration of Ultiva by TCI for the management of post-operative analgesia is not recommended.

Intensive Care - Adults
Ultiva can be used for the provision of analgesia in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.
It is recommended that Ultiva is initiated at an infusion rate of 0.1 microgram/kg/min (6 microgram/kg/h) to 0.15 microgram/kg/min (9 microgram/kg/h). The infusion rate should be titrated in increments of 0.025 microgram/kg/min (1.5 microgram/kg/h) to achieve the desired level of analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The level of sedation and analgesia should be carefully monitored, regularly reassessed and the Ultiva infusion rate adjusted accordingly. If an infusion rate of 0.2 microgram/kg/min (12 microgram/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent be 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 microgram/kg/min (1.5 microgram/kg/h) may be made if additional analgesia is required.
Ultiva 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.
Ultiva TCI has not been studied in intensive care patients and therefore administration of Ultiva by TCI is not recommended in these patients.
The following table summarises the starting infusion rates and typical dose range for provision of analgesia and sedation in individual patients.

DOSING GUIDELINES FOR USE OF ULTIVA WITHIN THE INTENSIVE CARE SETTING

CONTINUOUS INFUSION microgram/kg/min (microgram/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 Agent	Bolus (mg/kg)	Infusion (mg/kg/h)
Propofol	Up to 0.5	0.5
Midazolam	Up to 0.03	0.03

To allow separate titration of the respective agents sedative agents should not be administered as an admixture.
Additional analgesia for ventilated patients undergoing stimulating procedures: An increase in the existing 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 microgram/kg/min (6 microgram/kg/h) should be maintained for at least 5 minutes prior to the start of the stimulating procedure. Further dose adjustments may be made every 2 to 5 minutes in increments of 25%-50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 microgram/kg/min (15 microgram/kg/h), maximum 0.75 microgram/kg/min (45 microgram/kg/h), has been administered for provision of additional analgesia 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. 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, 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 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 μ-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 from 0.1 microgram/kg/min (6 microgram/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.

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

Renally-impaired intensive care patients
No adjustments to the doses recommended above are necessary in renally-impaired patients, including those undergoing renal replacement therapy, however the clearance of the carboxylic acid metabolite is reduced in patients with renal impairment.

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

Contraindications
- As glycine is present in the formulation Ultiva is contraindicated for epidural and intrathecal use.
- Ultiva is contraindicated in patients with known hypersensitivity to any component of the preparation and other fentanyl analogues.
- Ultiva is contra-indicated for use as the sole agent for induction of anaesthesia.

Special warnings and precautions for use
Ultiva 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 with all opioids, remifentanil is not recommended for use as the sole agent in general anaesthesia.

Rapid offset of action: Due to the very rapid offset of action of Ultiva, patients may emerge rapidly from anaesthesia and no residual opioid activity will be present within 5-10 minutes after the discontinuation of Ultiva. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to or immediately following 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.

Inadvertent administration: A sufficient amount of Ultiva 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 Ultiva into a fast flowing IV line or via a dedicated IV line which is adequately cleared of residual drug or which is removed when Ultiva is discontinued.

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

Respiratory depression - management: 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. 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, as many factors may affect post-operative recovery it is important to ensure that full consciousness and adequate spontaneous ventilation are achieved before the patient is discharged from the recovery area.

Cardiovascular effects: Hypotension and bradycardia (see Undesirable effects) may be managed by reducing the rate of infusion of Ultiva 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.

Interactions
The cardiovascular effects of Ultiva (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents.

Pregnancy and Lactation
There are no adequate and well-controlled studies in pregnant women. Ultiva should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Labour and Delivery
The safety profile of Ultiva during labour or delivery has not been demonstrated. There are insufficient data to recommend Ultiva for use during labour and caesarean section.
Caution should be exercised when Ultiva is administered to a nursing mother.

Undesirable effects
The most common adverse events associated with remifentanil are direct extensions of μ-opioid agonist pharmacology. These are acute respiratory depression, bradycardia, hypotension, post-operative hypertension and/or skeletal muscle rigidity. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil administration. Post-operative shivering, apnoea, hypoxia, pruritus, constipation, aches, sedation, nausea and vomiting have also been reported.
In common with other opioids, rare cases of asystole, usually preceded by bradycardia, have been reported in patients receiving remifentanil in association with other anaesthetic agents.
Rarely, allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents.

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 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 ten minutes.
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. 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 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.

PHARMACEUTICAL PARTICULARS

List of excipients
Glycine Ph. Eur.
Hydrochloric acid Ph. Eur.

Incompatibilities
Ultiva should only be admixed with those infusion solutions recommended (See Instructions for use/handling).
It should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Dextrose Injection.
Ultiva should not be mixed with propofol in the same intravenous admixture solution.
Administration of Ultiva into the same intravenous line with blood/serum/plasma is not recommended. Non-specific esterases in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.
Ultiva should not be mixed with other therapeutic agents prior to administration.

Special precautions for storage
Store at or below 25°C.
The reconstituted solution of Ultiva is chemically and physically stable for 24 hours at or below 25°C. However, Ultiva does not contain an antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions, reconstituted product should be used promptly, and any unused material discarded.

Instructions for use/handling
Ultiva is stable for 24 hours at room temperature after reconstitution and further dilution with one of the following IV fluids listed below:
- 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

For manually-controlled infusion Ultiva can be diluted to concentrations of 20 to 250 μg/ml (50 μg/ml is the recommended dilution for adults and 20 to 25 μg/ml for paediatric patients aged 1 year and over).
For TCI the recommended dilution of Ultiva is 20 to 50 μg/ml.
Ultiva has been shown to be compatible with the following intravenous 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.
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Parma, Italy
* Member of the GlaxoSmithKline group of companies

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers,

Union of Arab Pharmacists.

ان هذا الدواء

- الدواء مستحضر يؤثر على صحتك و استهلاكه خلافا للتعليمات يعرضك للخطر.
- اتبع بدقة وصفة الطبيب و طريقة الاستعمال المنصوص عليها و تعليمات الصيدلانى الذى صرفها لك.
- فالطبيب و الصيدلانى هما الخبيران بالدواء و بنفعه و ضرره.
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
- لا تكرر صرف الدواء بدون وصفة طبية.

لا تترك الأدوية فى متناول أيدى الأطفال

مجلس وزراء الصحة العرب
و اتحاد الصيادلة العرب

GlaxoSmithKline

10000000049113