SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ultiva 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed, solutions of Ultiva are clear and colourless and contain 1 mg/ml of remifentanil base as remifentanil hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for injection/infusion.
Ultiva is a sterile, non-pyrogenic, preservative-free, white to off white, lyophilised powder, to be reconstituted before use.

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see sections 4.4 and 4.5].
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
Limit dosages and durations to the minimum required.
Follow patients for signs and symptoms of respiratory depression and sedation.

4. CLINICAL PARTICULARS

4.1 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 and sedation in mechanically ventilated intensive care patients 18 years of age and over.

4.2 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.
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 (*see section 6.6* for additional information, including

tables with examples of infusion rates by body weight to help titrate Ultiva to the patient's anaesthetic needs).
Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual Ultiva after use (*see section 4.4*).
Ultiva is for intravenous use only and must not be administered by epidural or intrathecal injection (*see section 4.3*).

Dilution

Ultiva may be further diluted after reconstitution (*see sections 6.4 and 6.6* for storage conditions of the reconstituted/diluted product and the recommended diluents).
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).
(*See section 6.6* for additional information, including tables to help titrate Ultiva to the patient's anaesthetic needs).

4.2.1 General Anaesthesia

The administration of Ultiva must be individualised based on the patient's response. Specific dosing guidelines for patients undergoing cardiac surgery are provided in section 4.2.2 below.

4.2.1.1. Adults

Administration by Manually-Controlled Infusion

The following table summarises the starting 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 0.5 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 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 an increase of haemodynamic effects such as hypotension and bradycardia (see Concomitant medication below).

Induction of anaesthesia: Ultiva should be administered with a standard dose of a hypnotic agent, such as propofol, thiopentone, or isoflurane, for the induction of anaesthesia. Administering Ultiva after a hypnotic agent will reduce the incidence of muscle rigidity. 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 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 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 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.

Ultiva 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: Ultiva decreases the amounts or doses of inhaled anaesthetics, hypnotics and benzodiazepines required for anaesthesia (*see section 4.5*).

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

Guidelines for discontinuation/continuation 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.

Care should be taken to avoid inadvertent administration of Ultiva remaining in IV lines and cannulae (*see section 4.4*).

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 ventilated patients, the infusion rate should continue to be titrated to effect.

Guidance on provision of analgesia and sedation in mechanically ventilated intensive care patients is provided in section 4.2.3 below.

In patients who are breathing spontaneously, the infusion rate of Ultiva 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. 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.

4.2.1.2 Paediatric patients (2 to12 years of age)

Induction of anaesthesia: There are insufficient data to make a dosage recommendation.

4.2.2 Cardiac anaesthesia

Administration by Manually-Controlled Infusion

DOSING GUIDELINES FOR CARDIAC ANAESTHESIA

INDICATION	BOLUS INJECTION (micrograms/kg)	CONTINUOUS INFUSION (micrograms/kg/min)	
		Starting Rate	Range
Induction of anaesthesia	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 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 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 upward in 25% to 100% increments, or downward in 25% to 50% decrements, every 2 to 5 minutes according to patient need.

Supplemental slow bolus doses, administered over not less than 30 seconds, may also be given every 2 to 5 minutes 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*).

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 excessive depth of anaesthesia. No data are available for dosage recommendations for simultaneous use of other hypnotics other than those listed in the table with remifentanil (*see section 4.2.1.1* 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 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 (*see section 4.2.3* 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 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.

4.2.3 Use in Intensive Care

Ultiva can be used for the provision of analgesia in mechanically ventilated intensive care patients. Sedative agents should be added as appropriate.
Ultiva has been studied in mechanically ventilated intensive care patients in well controlled clinical trials for up to three days. As patients were not studied beyond three days, no evidence of safety and efficacy for longer treatment has been established. Therefore, 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 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 sedation and analgesia. A period of at least 5 minutes should be allowed between dose adjustments. The level of sedation and analgesia should be carefully monitored, regularly reassessed and the Ultiva infusion rate adjusted accordingly. If an infusion rate of 0.2 micrograms/kg/min (12 micrograms/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative agent is initiated (see below). The dose of 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 and sedation 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 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 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%-50% in anticipation of, or in response to, additional requirement for analgesia. A mean infusion rate of 0.25 micrograms/kg/min (15 micrograms/kg/h), maximum 0.75 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 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, 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 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 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 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.

4.2.3.1 Paediatric intensive care 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.

4.2.3.2 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*).

4.2.4 Special patient populations

4.2.4.1 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.

Cardiac anaesthesia: No initial dose reduction is required (*see section 4.2.2.*).

Intensive Care: No initial dose reduction is required (*see section 4.2.3.*).

4.2.4.2 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.

4.2.4.3 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.

4.2.4.4 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*). These patients shall be closely monitored and the dose of remifentanil shall be titrated to individual patient need.

4.2.4.5 Neurosurgery

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

4.2.4.6 ASA III/IV patients

General anaesthesia: As the haemodynamic effects of potent opioids can be expected to be more pronounced in ASA III/IV patients, caution should be exercised in the administration of 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 (*see section 4.2.2*).

4.3 Contraindications

As glycine is present in the formulation, Ultiva is contraindicated for epidural and intrathecal use.

Hypersensitivity to the active substance, other fentanyl analogues, or to any of the excipients listed in section 6.1.

Ultiva is contraindicated for use as the sole agent for induction of anaesthesia.

4.4 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. The use of Ultiva in mechanically ventilated intensive care patients is not recommended for a duration of treatment greater than 3 days.

Patients with a known hypersensitivity to opioids of a different class may exhibit a hypersensitivity reaction following administration of Ultiva. Caution should be exercised before using Ultiva in these patients.

Rapid offset of action /Transition to alternative analgesia

Due to the very rapid offset of action of Ultiva, no residual opioid activity will be present within 5 to 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 discontinuation of Ultiva. The possibility of tolerance, hyperalgesia and associated haemodynamic changes should be considered when used in Intensive Care Unit. Prior to discontinuation of Ultiva, patients must be given alternative analgesic and sedative agents. 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. When other opioid agents are administered as part of the regimen for transition to alternative analgesia, the benefit of providing adequate post-operative analgesia must always be balanced against the potential risk of respiratory depression with these agents.

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

Concomitant use of Ultiva and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not

possible. If a decision is made to prescribe Ultiva concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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

Discontinuation of Treatment and withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy.
Symptoms following withdrawal of Ultiva including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of Ultiva in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

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

Respiratory depression – prevention and 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

The risk of cardiovascular effects such as hypotension and bradycardia (*see section 4.8*), which may rarely lead to asystole/cardiac arrest may be reduced by lowering 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.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

4.5 Interaction with other medicinal products and other forms of interaction

Remifentanil is not metabolised by plasmacholinesterase, therefore, interactions with drugs metabolised by this enzyme are not anticipated.

As with other opioids, remifentanil, whether given by manually-controlled infusion, decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia (*see section 4.2* Posology and method of administration, General Anaesthesia – Adults, Paediatric Patients, and Cardiac Surgery). If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents.

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (*see section 4.4*). The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Co-administration of remifentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Monoamine Oxidase Inhibitors (MAOIs) may increase the risk of serotonin syndrome, a potentially life-threatening condition. Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to remifentanil
use.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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

For a summary of the reproductive toxicity study findings please refer to Section 5.3 Preclinical safety data.

Labour and delivery

The safety profile of remifentanil during labour or delivery has not been demonstrated. There are insufficient data to recommend remifentanil for use during labour and Caesarean section. Remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child. In case remifentanil is administered nevertheless, the patient and the neonate must be monitored for signs of excess sedation or respiratory depression (see section 4.4).

4.7 Effects on ability to drive and use machines

After anaesthesia with remifentanil the patient should not drive or operate machinery. The physician should decide when these activities may be resumed. It is advisable that the patient is accompanied when returning home and that alcoholic drink is avoided.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely.

4.8 Undesirable effects

Summary of the safety profile

The most common undesirable effects associated with remifentanil are direct extensions of mu-opioid agonist pharmacology. These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil administration.

Tabulated list of adverse reactions

The frequencies below are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Immune System Disorders	Rare	Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic agents
Psychiatric disorders	Not known	Drug dependence, withdrawal syndrome
Nervous System Disorders	Very common	Skeletal muscle rigidity
	Rare	Sedation (during recovery from general anaesthesia)
	Not known	Convulsions
Cardiac Disorders	Common	Bradycardia
	Rare	Asystole/cardiac arrest, usually preceded by bradycardia, has been reported in patients receiving remifentanil in conjunction with other anaesthetic agents
	Not known	Atrioventricular block, arrhythmia
Vascular Disorders	Very common	Hypotension
	Common	Post-operative hypertension
Respiratory, Thoracic and Mediastinal Disorders	Common	Acute respiratory depression, apnoea, cough
	Uncommon	Hypoxia
Gastrointestinal Disorders	Very common	Nausea, vomiting
	Uncommon	Constipation
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
General Disorders and Administration Site Conditions	Common	Post-operative shivering
	Uncommon	Post-operative aches
	Not known	Drug tolerance

Discontinuation of treatment

Symptoms following withdrawal of remifentanil including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days (*see section 4.4*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il.
Additionally, you may also report to: Padagis.co.il.

4.9 Overdose

Symptoms
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 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.

Management
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 in addition to ventilatory support to manage severe respiratory depression. The duration of respiratory depression following overdose with Ultiva is unlikely to exceed the duration of action of the opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH06

Remifentanil is a selective mu-opioid agonist with a rapid onset and very short duration of action. The mu-opioid activity of remifentanil is antagonised by narcotic antagonists, such as naloxone.

Assays of histamine in patients and normal volunteers have shown no elevation in histamine levels after administration of remifentanil in bolus doses up to 30 micrograms/kg.

Neonates/infants (aged less than 1 year):
In a randomised (ratio of 2:1, remifentanil:halothane), open label, parallel group, multicentre study in 60 young infants and neonates ≤8 weeks of age (mean 5.5 weeks) with an ASA physical status of I-II who were undergoing pyloromyotomy, the efficacy and safety of remifentanil (given as a 0.4 μg/kg/min initial continuous infusion plus supplemental doses or infusion rate changes as needed) was compared with halothane (given at 0.4% with supplemental increases as needed). Maintenance of anaesthesia was achieved by the additional administration of 70% nitrous oxide (N_20) plus 30% oxygen. Recovery times were superior in the remifentanil relative to the halothane groups (not significant).

Use for Total Intravenous Anaesthesia (TIVA) - children aged 6 months to 16 years

TIVA with remifentanil in paediatric surgery was compared to inhalation anaesthesia in three randomised, open-label studies. The results are summarised in the table below.

Surgical intervention	**Age (y), (N)**	**Study condition (maintenance)**	**Extubation (min) (mean (SD))**
Lower abdominal/urological surgery	0.5-16 (120)	TIVA: propofol (5 - 10 mg/kg/h) + remifentanil (0.125 - 1.0 μg/kg/min)	11.8 (4.2)
		Inhalation anaesthesia: sevoflurane (1.0 - 1.5 MAC) and remifentanil (0.125 - 1.0 μg/kg/min)	15.0 (5.6) ($p<0.05$)
ENT-surgery	4-11 (50)	TIVA: propofol (3 mg/kg/h) + remifentanil (0.5 μg/kg/min)	11 (3.7)
		Inhalation anaesthesia: desflurane (1.3 MAC) and N_2O mixture	9.4 (2.9) Not significant
General or ENT surgery	2-12 (153)	TIVA: remifentanil (0.2 - 0.5 μg/kg/min) + propofol (100 - 200 μg/kg/min)	Comparable extubation times (based on limited data)
		Inhalation anaesthesia: sevoflurane (1 - 1.5 MAC) + N_2O mixture	

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

5.2 Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg, the central volume of distribution is 100 ml/kg and the steady-state volume of distribution is 350 ml/kg. In children aged 1 to 12 years, remifentanil clearance and volume of distribution decreases with increasing age; the values of these parameters in neonates are approximately twice those of healthy young adults.

Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 micrograms/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5nanograms/ml. Remifentanil is approximately 70% bound to plasma proteins.

Biotransformation

Remifentanil is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite (1/4600th as potent as remifentanil). The half life of the metabolite in healthy adults is 2 hours. Approximately 95% of remifentanil is recovered in the urine as the carboxylic acid metabolite. Remifentanil is not a substrate for plasma cholinesterase.

Cardiac anaesthesia

The clearance of remifentanil is reduced by approximately 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree centigrade.

Renal impairment

The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status.

The pharmacokinetics of remifentanil is not significantly changed in patients with varying degrees of renal impairment even after administration for up to 3 days in the intensive care setting.

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. Especially in intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite may exceed 250-fold the level of remifentanil at steady-state in some patients. Clinical data demonstrate that the accumulation of the metabolite does not result in clinically relevant mu -opioid effects even after administration of remifentanil infusions for up to 3 days in these patients.

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

The carboxylic acid metabolite is extracted during haemodialysis by 25 - 35 %.

Hepatic impairment

The pharmacokinetics of remifentanil is not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored and the dose of remifentanil should be titrated to the individual patient need.

Paediatric patients

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

Elderly

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

Placental and milk transfer

In a human clinical trial, the mean ratio of maternal arterial to umbilical venous concentration indicated that the neonate was exposed to approximately 50% concentration of remifentanil to that in the mother. The mean umbilical arterio-venous ratio of remifentanil concentrations was approximately 30% suggesting metabolism of remifentanil in the neonate.

5.3 Preclinical safety data

Intrathecal administration of the glycine formulation without remifentanil to dogs caused agitation, pain and hind limb dysfunction and incoordination. These effects are believed to be secondary to the glycine excipient. Glycine is a commonly used excipient in intravenous products and this finding has no relevance for intravenous administration of Ultiva.

Remifentanil, like other opioid agonists, produced increases in action potential duration (APD) in dog isolated Purkinje fibres. For remifentanil, the effects were seen at concentrations of 1μM or higher (which are higher than plasma concentrations seen in clinical practice). There were no effects at a concentration of 0.1μM.

The major metabolite remifentanil acid had no effect on APD up to the maximum tested concentration of 10μM.

Reproductive toxicity studies

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

Genotoxicity

Remifentanil was devoid of genotoxic activity in bacteria and in rat liver or mouse bone marrow cells in vivo. However, a positive response was seen in vitro in different mammalian cell systems in the presence of a metabolic activation system. This activity was seen only at concentrations more than three orders of magnitude higher than therapeutic blood levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Ultiva should only be reconstituted and diluted with those infusion solutions recommended (*see section 6.*).

It should not be reconstituted, diluted or mixed with Lactated Ringer's Injection or Lactated Ringer's and 5% Dextrose Injection.

Ultiva should not be mixed with propofol in the same infusion bag prior to administration.

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.

6.3 Shelf-life

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Do not store above 25ºC.
The reconstituted solution of Ultiva is chemically and physically stable for 24 hours at room temperature (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.

6.5 Nature and contents of container

Ultiva 5 mg is available as 5 mg of Remifentanil lyophilised powder in 10 ml vials, in cartons of 5.

6.6 Special precautions for disposal and other handling

Ultiva 5mg should be prepared for intravenous use by adding, as appropriate, 5 ml of diluent to give a reconstituted solution with a concentration of 1mg/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.

Ultiva 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).

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.

Ultiva 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

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.

The following tables give guidelines for infusion rates of Ultiva for manually-controlled infusion:

Table 1. Ultiva for Injection Infusion Rates (ml/kg/h)

Drug Delivery Rate (micrograms/kg/min)	Infusion Delivery Rate (ml/kg/h) for Solution Concentrations of		
	25 micrograms/ml 1 mg/40 ml	50 micrograms/ml 1 mg/20 ml	250 micrograms/ml 10 mg/40 ml
0.0125	0.03	0.015	Not recommended
0.025	0.06	0.03	Not recommended
0.05	0.12	0.06	0.012
0.075	0.18	0.09	0.018
0.1	0.24	0.12	0.024
0.15	0.36	0.18	0.036
0.2	0.48	0.24	0.048
0.25	0.6	0.3	0.06
0.5	1.2	0.6	0.12
0.75	1.8	0.9	0.18
1.0	2.4	1.2	0.24
1.25	3.0	1.5	0.3
1.5	3.6	1.8	0.36
1.75	4.2	2.1	0.42
2.0	4.8	2.4	0.48

Table 2. Ultiva for Injection Infusion Rates (ml/h) for a 20 micrograms/ml Solution

Infusion Rate(micrograms/kg/min)	Patient Weight (kg)						
	5	10	20	30	40	50	60
0.0125	0.188	0.375	0.75	1.125	1.5	1.875	2.25
0.025	0.375	0.75	1.5	2.25	3.0	3.75	4.5
0.05	0.75	1.5	3.0	4.5	6.0	7.5	9.0
0.075	1.125	2.25	4.5	6.75	9.0	11.25	13.5
0.1	1.5	3.0	6.0	9.0	12.0	15.0	18.0
0.15	2.25	4.5	9.0	13.5	18.0	22.5	27.0
0.2	3.0	6.0	12.0	18.0	24.0	30.0	36.0
0.25	3.75	7.5	15.0	22.5	30.0	37.5	45.0
0.3	4.5	9.0	18.0	27.0	36.0	45.0	54.0

0.35	5.25	10.5	21.0	31.5	42.0	52.5	63.0
0.4	6.0	12.0	24.0	36.0	48.0	60.0	72.0

Table 3. Ultiva for Injection Infusion Rates (ml/h) for a 25 micrograms/ml Solution

Infusion Rate (micrograms /kg/min)	**Patient Weight (kg)**									
	10	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.0125	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.025	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.05	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.075	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.1	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.15	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
0.2	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4	43.2	48.0

Table 4. Ultiva for Injection Infusion Rates (ml/h) for a 50 micrograms/ml Solution

Infusion Rate (micrograms /kg/min)	**Patient Weight (kg)**							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.025	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
0.05	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
0.075	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0
0.1	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
0.15	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
0.2	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
0.25	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0
0.5	18.0	24.0	30.0	36.0	42.0	48.0	54.0	60.0
0.75	27.0	36.0	45.0	54.0	63.0	72.0	81.0	90.0
1.0	36.0	48.0	60.0	72.0	84.0	96.0	108.0	120.0
1.25	45.0	60.0	75.0	90.0	105.0	120.0	135.0	150.0
1.5	54.0	72.0	90.0	108.0	126.0	144.0	162.0	180.0
1.75	63.0	84.0	105.0	126.0	147.0	168.0	189.0	210.0
2.0	72.0	96.0	120.0	144.0	168.0	192.0	216.0	240.0

Table 5. Ultiva for Injection Infusion Rates (ml/h) for a 250 micrograms/ml Solution

Infusion Rate (micrograms /kg/min)	Patient Weight (kg)							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
0.1	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40
0.15	1.08	1.44	1.80	2.16	2.52	2.88	3.24	3.60
0.2	1.44	1.92	2.40	2.88	3.36	3.84	4.32	4.80
0.25	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
0.5	3.60	4.80	6.00	7.20	8.40	9.60	10.80	12.00
0.75	5.40	7.20	9.00	10.80	12.60	14.40	16.20	18.00
1.0	7.20	9.60	12.00	14.40	16.80	19.20	21.60	24.00
1.25	9.00	12.00	15.00	18.00	21.00	24.00	27.00	30.00
1.5	10.80	14.40	18.00	21.60	25.20	28.80	32.40	36.00
1.75	12.60	16.80	21.00	25.20	29.40	33.60	37.80	42.00
2.0	14.40	19.20	24.00	28.80	33.60	38.40	43.20	48.00

7. Manufacturer

GlaxoSmithKline Manufacturing S.p.A, Parma, Italy.

8. Registration Holder

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9. License Number

Ultiva 5 mg 108-35-29195-22

Revised in November 2022 according to MOH guidelines

20/11/2022