1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S6

PROPRIETARY NAME AND DOSAGE FORM

FORTIVA 1 mg (injection)

FORTIVA 2 mg (injection)

FORTIVA 5 mg (injection)

COMPOSITION

Each vial of FORTIVA 1 mg, contains 1 mg remifentanil base as remifentanil hydrochloride.

Each vial of FORTIVA 2 mg, contains 2 mg remifentanil base as remifentanil hydrochloride.

Each vial of FORTIVA 5 mg, contains 5 mg remifentanil base as remifentanil hydrochloride.

Excipient:

Glycine

Sugar free

CATEGORY AND CLASS

A 2.9 Other analgesics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3 to 10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg. Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0,1 μg/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2,5 ng/ml. Remifentanil is approximately 70 % bound to plasma proteins.

Metabolism: 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 (1/4 600th 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.

Placental and milk transfer: Remifentanil crosses the placenta and appears in breast milk.

In a human clinical trial, the concentration of remifentanil in foetal blood was approximately

50 % of that in maternal blood.

The foetal arterio-venous ratio of remifentanil concentrations was approximately 30 %, suggesting metabolism of remifentanil in the neonate.

Cardiac anaesthesia: The clearance of remifentanil is reduced by up to 20 % during hypothermic (28 °C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3 % per degree Celsius.

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

The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment, the concentration of the carboxylic acid metabolite is expected to reach approximately 100-fold the level of remifentanil at steady state. Clinical data demonstrates that accumulation of the metabolite does not result in clinically relevant μ-opioid effects even after administration of remifentanil infusions for up to 3 days in these patients.

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

The carboxylic acid metabolite is extracted during haemodialysis by at least 30 %.

Hepatic impairment: The pharmacokinetics of remifentanil are 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 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: In paediatric patients 5 days to 17 years of age, 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 half-life of remifentanil is not significantly different in neonates suggesting that changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to that seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2 to 17 years of age are similar to those seen in adults after correcting for differences in body weight.

Elderly: The clearance of remifentanil is slightly reduced (approx. 25 %) in elderly patients (> 65 years) compared to young patients.

Elderly patients have a remifentanil EC_{50} for the formation of delta waves on the EEG that is 50 % lower than young patients do; therefore, the initial dose of remifentanil should be reduced by 50 % in elderly patients and then carefully titrated to meet the individual patient need.

INDICATIONS

FORTIVA is indicated as a narcotic analgesic or adjuvant for use during induction and/or maintenance of inhalational anaesthesia during surgical procedures including cardiac surgery.

FORTIVA is indicated for the provision of analgesia and as an aid to sedation (up to 72 hours sedation) in mechanically ventilated intensive care patients. Safety and efficacy beyond 72 hours has not been demonstrated.

CONTRAINDICATIONS

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

Known hypersensitivity to any component of FORTIVA, and other fentanyl analogues.

Safety in pregnancy and lactation has not been established.

FORTIVA should not be used with nitrous oxide and oxygen alone at altitudes above sea level.

FORTIVA should not be used unless artificial ventilation is planned.

WARNINGS AND SPECIAL PRECAUTIONS

FORTIVA is not recommended for use as the sole medicine in general anaesthesia.

FORTIVA should be administered only by persons specifically trained in the use of anaesthetics and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation such as the establishment and maintenance of a patent airway and assisted ventilation.

Inadvertent administration: A sufficient amount of FORTIVA 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 medicines. This may be avoided by administering FORTIVA into a fast-flowing IV line or via a dedicated IV line, which is adequately cleared of residual medicine or which is removed upon discontinuation of FORTIVA.

FORTIVA may produce dependency.

The safety profile of FORTIVA during labour or delivery has not been demonstrated. There are insufficient data to recommend FORTIVA for use during labour and caesarean section.

Remifentanil, as contained in FORTIVA, crosses the placental barrier and fentanyl analogues can cause respiratory depression in the baby.

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

Muscle rigidity - prevention and management: At the doses recommended muscle rigidity may occur. The incidence is related to the dose and rate of administration. Therefore, bolus infusions should be administered over not less than 30 seconds.

Muscle rigidity induced by FORTIVA must be treated in the context of the patient's clinical

condition with appropriate supporting measures.

Excessive muscle rigidity occurring during the induction of anaesthesia should be treated by the administration of a neuromuscular blocking medicine and/or additional hypnotic medicines.

Muscle rigidity seen during the use of FORTIVA as an analgesic may be treated by stopping or decreasing the rate of administration of FORTIVA. Resolution of muscle rigidity after discontinuing the infusion of FORTIVA occurs within minutes.

Respiratory depression - management: Analgesia is accompanied by marked respiratory depression. Therefore, FORTIVA 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 a discontinuation of the infusion. Remifentanil, as contained in FORTIVA, 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 may be managed by reducing the rate of infusion of FORTIVA or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic medicines as appropriate.

Debilitated, hypovolaemic and elderly patients are more sensitive to the cardiovascular effects of remifentanil, as contained in FORTIVA.

Effects on ability to drive and use machines

If an early discharge is envisaged following treatment using anaesthetic medicines, patients should be advised not to drive or operate machinery.

INTERACTIONS

Remifentanil, as contained in FORTIVA, is not metabolised by plasmacholinesterase and therefore interactions with medication metabolised by this enzyme are not anticipated.

If doses of concomitantly administered CNS depressant medicines are not reduced, patients may experience an increased incidence of adverse effects associated with these medicines.

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

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established.

Placental and milk transfer: Remifentanil crosses the placenta and appears in breast milk (see PHARMACOLOGICAL ACTION).

DOSAGE AND DIRECTIONS FOR USE

Continuous infusion of FORTIVA 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.

Care should be taken to avoid obstruction or disconnection of infusion lines and to adequately clear the lines to remove residual FORTIVA after use (see WARNINGS AND SPECIAL PRECAUTIONS).

FORTIVA is for intravenous use only and must not be administered by epidural or intrathecal injection (see CONTRAINDICATIONS).

Reconstitution:

The reconstituted solution is stable for 24 hours at room temperature (25 °C) and further dilution to 20 µg/ml to 250 µg/ml (50 µg/ml is the recommended dilution for adults and 20 µg/ml to 25 µg/ml for paediatric patients aged 1 year and over) with one of the following IV fluids 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

FORTIVA should not be admixed with Lactated Ringer's Injection or Lactated Ringer's and 5 % Dextrose Injection, but it has shown to be compatible with these IV fluids when administered into a running IV catheter.

FORTIVA should not be administered into the same intravenous line with blood/serum/plasma as non-specific esterases in blood products may lead to the hydrolysis of remifentanil to its inactive metabolite.

FORTIVA should not be mixed with other therapeutic medicines prior to administration.

GENERAL ANAESTHESIA

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

Adults:

The following table summarises the starting infusion rates and dosage range:

Dosing Guidelines For Adults

INDICATION	**BOLUS INFUSION OF FORTIVA (µg/kg)**	**CONTINUOUS INFUSION OF FORTIVA (µg/kg/min)**	
		Starting Rate	**Range**
With Induction of anaesthesia in ventilated patients	1 (given over not less than 30 seconds)	0,5 to 1,0	
Maintenance of anaesthesia in ventilated patients			
• Isoflurane (starting dose 0,5 MAC)	0,5 to 1,0	0,25	0,05 to 0,5

At the doses recommended, FORTIVA significantly reduces the amount of hypnotic medicine required to maintain anaesthesia. Therefore, isoflurane should be administered as recommended above to avoid excessive depth of anaesthesia (see INTERACTIONS).

Induction of anaesthesia: FORTIVA should be administered with a hypnotic medicine, such as isoflurane, for the induction of anaesthesia. FORTIVA can be administered at an infusion rate of 0,5 µg/kg/min to 1,0 µg/kg/min with or without an initial bolus infusion of 1 µg/kg over not less than 30 seconds. If endotracheal intubation is to occur more than 8 to 10 minutes after the start of the FORTIVA infusion, then a bolus infusion is not necessary.

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

Guidelines for discontinuation: Due to the very rapid offset of action of FORTIVA, residual opioid activity will be reduced 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, or immediately following discontinuation of FORTIVA. 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.

Paediatric patients (1 to 12 years of age):

Induction of anaesthesia: FORTIVA is not recommended for the induction of anaesthesia, as insufficient data are available.

Maintenance of anaesthesia:

CONCOMITANT ANAESTHETIC MEDICINE	BOLUS INFUSION OF FORTIVA (µg/kg)	CONTINUOUS INFUSION OF FORTIVA (µg/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

When given by bolus infusion, FORTIVA should be administered over not less than 30 seconds.

Surgery should not commence until at least 5 minutes after the start of the FORTIVA infusion, if a simultaneous bolus dose has not been given. 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, FORTIVA significantly reduces the amount of hypnotic medicine 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, as contained in FORTIVA.

Guidelines for discontinuation: Following discontinuation of the infusion, the offset of analgesic effect of FORTIVA is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be anticipated and implemented (see Adults -

Guidelines for discontinuation).

Neonates/infants (aged less than 1 year): The pharmacokinetic profile of remifentanil, as contained in FORTIVA, in neonates/infants (aged less than 1 year) is comparable to that seen in adults after correction of body weight differences. However, there are insufficient clinical data to make dosage recommendations for this age group.

CARDIAC ANAESTHESIA

Adults:

Dosing Guidelines For Cardiac Anaesthesia

INDICATION	**BOLUS INFUSION OF FORTIVA (µg/kg)**	**CONTINUOUS INFUSION OF FORTIVA (µg/kg/min)**	
		Starting Rate	Typical Infusion Rates
Intubation	Not recommended	1	-
Maintenance of anaesthesia			
• Isoflurane (starting dose 0,4 MAC)	0,5 to 1	1	0,003 to 4
• Propofol (starting dose 50 µg/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, FORTIVA should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus infusions of FORTIVA 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 FORTIVA should be titrated according to patient need. Supplemental 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 µg/kg. These dosing recommendations also apply during hypothermic cardiopulmonary bypass (see Pharmacokinetic Properties - Cardiac anaesthesia).

Concomitant medication: At the doses recommended above, FORTIVA significantly reduces the amount of hypnotic medicine 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 with FORTIVA.

Continuation of post-operative analgesia prior to extubation: It is recommended that the infusion of FORTIVA 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 infusion should be maintained initially at a rate of 1 µg/kg/min until the patient is ready to be weaned from the ventilator.

Guidelines for discontinuation: Prior to discontinuation of FORTIVA patients must be given alternative analgesic and sedative medicine at a sufficient time in advance. The choice and

dose of medicine(s) should be appropriate for the patient's level of post-operative care.

It is recommended that the FORTIVA infusion is discontinued by reducing the infusion rate in three or four steps of 50 % at 10-minute intervals.

During weaning from the ventilator, the FORTIVA infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

It is recommended that haemodynamic changes such as hypertension and tachycardia should be treated with alternative medicines as appropriate.

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

USE IN INTENSIVE CARE

FORTIVA can be used for the provision of analgesia for up to 72 hours and short-term sedation in mechanically ventilated intensive care patients.

It is recommended that FORTIVA is initiated at an infusion rate of 0,1 µg/kg/min (6 µg/kg/h) to 0,15 µg/kg/min (9 µg/kg/h). The infusion rate should be titrated in increments of 0,025 µg/kg/min (1,5 µg/kg/h) to achieve the desired level of analgesia and sedation. A period of at least 5 minutes should be allowed between dose adjustments. The level of analgesia and sedation should be carefully monitored, regularly reassessed and the FORTIVA infusion rate adjusted accordingly. If an infusion rate of 0,2 µg/kg/min (12 µg/kg/h) is reached and the desired level of sedation is not achieved, it is recommended that dosing with an appropriate sedative medicine is initiated (see below). The dose of sedative medicine should be titrated to obtain the desired

level of sedation. Further increases to the FORTIVA infusion rate in increments of 0,025 µg/kg/min (1,5 µg/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 FORTIVA Within The Intensive Care Setting

CONTINUOUS INFUSION µg/kg/min (µg/kg/h)	
Starting Rate	Range
0,1(6) to 0,15 (9)	0,006 (0,36) to 0,74 (44,4)

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

The use of FORTIVA will reduce the dosage requirement of any concomitant sedative medicines by approximately 50 %. Typical starting doses for sedative medicines, if required, are given below.

Recommended starting dose of sedative medicines, if required:

Sedative medicine	**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 medicines, sedative medicines should not be administered as an admixture via the same infusion set.

Additional analgesia for ventilated patients undergoing stimulating procedures: An

increase in the existing FORTIVA infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that a FORTIVA infusion rate of at least 0,1 µg/kg/min (6 µg/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 µg/kg/min (15 µg/kg/h), maximum 0,75 µg/kg/min (45 µg/kg/h), has been administered for provision of additional anaesthesia during stimulating procedures.

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

Guidelines for extubation and discontinuation of FORTIVA: In order to ensure a smooth emergence from a FORTIVA-based regimen it is recommended that the infusion rate of FORTIVA is titrated in stages to 0,1 µg/kg/min (6 µg/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 FORTIVA infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

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

When other opioid medicines 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 medicines.

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.

SPECIAL PATIENT POPULATIONS

Elderly (over 65 years of age):

General anaesthesia: The initial starting dose of remifentanil, as contained in FORTIVA, should be half the recommended adult dose and then 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 Cardiac Anaesthesia - Dosing guidelines).

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

Obese patients:

For obese patients (greater than 30 % over their ideal body weight) the dosage of FORTIVA should be reduced and based upon ideal body weight as the clearance and volume of distribution of remifentanil, as contained in FORTIVA, are better correlated with ideal body weight than actual body weight in this population.

Renal impairment:

No dosage adjustment is necessary in patients with impaired renal function, including intensive care patients.

Hepatic impairment:

No dosage adjustment is necessary. However, patients with severe hepatic impairment may be more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely monitored, and the dose of remifentanil, as contained in FORTIVA, titrated to individual patient need.

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 FORTIVA in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

Cardiac anaesthesia: No initial dose reduction is required (see Cardiac Anaesthesia - Dosing

guidelines).

Long-term use in the ICU: No data are available on the long-term (longer than 24 hours) use of FORTIVA in ICU patients.

SIDE EFFECTS

The most common adverse events associated with FORTIVA are direct extensions of μ-opioid agonist pharmacology.

The overall reporting incidence, as determined from all phases of controlled anaesthesia studies at recommended doses, is as follows:

Very common (≥ 10 %)	Nausea, vomiting, hypotension, skeletal muscle rigidity.
Common (Frequent) (≥ 1 % and < 10 %)	Post-operative shivering, bradycardia, acute respiratory depression, apnoea, post-operative hypertension, pruritus.
Uncommon (Infrequent) (≥ 0,1 % and < 1 %)	Hypoxia, constipation, post-operative aches.
Rare (< 0,1 %)	Sedation (during recovery from general anaesthesia).

These adverse events resolve within minutes of discontinuing or decreasing the rate of remifentanil, as contained in FORTIVA, administration.

The following adverse events and reporting frequencies have been determined from post-marketing reporting:

- Allergic reactions including anaphylaxis have been reported in patients receiving FORTIVA in conjunction with one or more anaesthetic medicines.
- Cases of cardiac arrest, asystole usually preceded by bradycardia, have been reported in patients receiving FORTIVA in conjunction with other anaesthetic medicines.

Patients with severe hepatic impairment are more sensitive to the respiratory depressant effects.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Overdose would be manifested by an extension of the pharmacological actions of FORTIVA i.e. respiratory depression, bradycardia, hypotension and skeletal muscle rigidity.

Due to the very short duration of action of FORTIVA, the potential for overdose is limited to the immediate time period following administration. Response to discontinuation is rapid with return to baseline within ten minutes.

Treatment

In the event of overdosage, the following actions are to be taken:

- discontinue administration of FORTIVA,
- maintain a patent airway,
- initiate assisted or controlled ventilation with oxygen,
- maintain adequate cardiovascular function.

If depressed respiration is associated with muscle rigidity, a neuromuscular blocking medicine

may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressor medicines for the treatment of hypotension and other supportive measures may be employed.

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

IDENTIFICATION

White to off-white cake that may be intact or fragmented.

The reconstituted solution is a clear and colourless liquid, practically free from particulate matter.

PRESENTATION

FORTIVA 1 mg: 3 ml clear, Type 1 glass vials with grey bromobutyl rubber stoppers and secured with an aluminium overseal with a light blue plastic flip-off top. The vials are placed in a carboard carton together with a leaflet.

FORTIVA 2 mg: 5 ml clear, Type 1 glass vials with grey bromobutyl rubber stoppers and secured with an aluminium overseal with a royal blue plastic flip-off top. The vials are placed in a carboard carton together with a leaflet.

FORTIVA 5 mg: 10 ml clear, Type 1 glass vials with grey bromobutyl rubber stoppers and

secured with an aluminium overseal with a dark blue plastic flip-off top. The vials are placed in a carboard carton together with a leaflet.

Not all strengths, packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Keep in original packaging until required for use.

The reconstituted solution is stable for 24 hours at 25 °C.

Any unused portion must be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

FORTIVA 1 mg: 42/2.9/0751

FORTIVA 2 mg: 42/2.9/0752

FORTIVA 5 mg: 42/2.9/0753

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

PHARMACARE LIMITED

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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