PROFESSIONAL INFORMATION

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

REMIFENTANIL 1 mg ADCO powder for solution for IV Injection

REMIFENTANIL 2 mg ADCO powder for solution for IV Injection

REMIFENTANIL 5 mg ADCO powder for solution for IV Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REMIFENTANIL 1 mg ADCO

Each **REMIFENTANIL 1 mg ADCO** vial contains remifentanil hydrochloride equivalent to 1 mg remifentanil base.

REMIFENTANIL 2 mg ADCO

Each **REMIFENTANIL 2 mg ADCO** vial contains remifentanil hydrochloride equivalent to 2 mg remifentanil base.

REMIFENTANIL 5 mg ADCO

Each **REMIFENTANIL 5 mg ADCO** vial contains remifentanil hydrochloride equivalent to 5 mg remifentanil base.

Sugar content: Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for IV injection.

A white to off-white powder.

Reconstituted solutions are clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

REMIFENTANIL ADCO 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 have not been demonstrated.

4.2 Posology and method of administration

Posology

GENERAL ANAESTHESIA:

The administration of **REMIFENTANIL ADCO** must be individualised based on the patient's response.

Adults:

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

DOSAGE GUIDELINES FOR ADULTS:

INDICATION	BOLUS INFUSION OF REMIFENTANIL ADCO (µg/kg)	CONTINUOUS INFUSION OF REMIFENTANIL ADCO (µg/kg/min)	
		Starting rate	Range
With induction of anaesthesia in ventilated patients	1 (give 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, **REMIFENTANIL ADCO** 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 section 4.5).

Induction of anaesthesia:

REMIFENTANIL ADCO should be administered with a hypnotic medicine, such as isoflurane, for the induction of anaesthesia. **REMIFENTANIL ADCO** can be administered at an infusion rate of 0,5 – 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 **REMIFENTANIL ADCO** infusion, then a bolus infusion is not necessary.

Maintenance of anaesthesia:

After endotracheal intubation, the infusion rate of **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** the rate of administration during anaesthesia can be titrated upwards in 25 – 100 % increments or downwards in 25 – 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 rapid offset of action of **REMIFENTANIL ADCO**, 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 **REMIFENTANIL ADCO**. Sufficient time must be allowed to reach 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 – 12 years of age):

Induction of anaesthesia:

REMIFENTANIL ADCO is not recommended for the induction of anaesthesia, as insufficient data are available.

Maintenance of anaesthesia:

DOSAGE GUIDELINES FOR MAINTENANCE OF ANAESTHESIA IN PAEDIATRIC PATIENTS (1 – 12 years of age)

CONCOMITANT ANAESTHETIC MEDICINE	BOLUS INFUSION OF REMIFENTANIL ADCO (µg/kg)	CONTINUOUS INFUSION OF REMIFENTANIL ADCO (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, **REMIFENTANIL ADCO** should be administered over not less than 30 seconds.

Surgery should not commence until at least 5 minutes after the start of the **REMIFENTANIL ADCO** 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, **REMIFENTANIL ADCO** significantly reduces the amount of hypnotic medicine required to maintain anaesthesia. Therefore, halogenated anaesthetics 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 ADCO**.

Guidelines for discontinuation:

Following discontinuation of the infusion, the offset of analgesic effect of **REMIFENTANIL ADCO** is rapid and similar to that seen in adult patients. Appropriate post-operative analgesic requirements should be anticipated and implemented (see section **4.2 Adults – Guidelines for discontinuation**).

Neonates/infants (aged less than 1 year):

The pharmacokinetic profile of **REMIFENTANIL ADCO** 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:

DOSAGE GUIDELINES FOR CARDIAC ANAESTHESIA:

INDICATION	BOLUS INFUSION OF REMIFENTANIL ADCO (µg/kg)	CONTINUOUS INFUSION OF REMIFENTANIL ADCO (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 of 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 medicine to achieve loss of consciousness, **REMIFENTANIL ADCO** should be administered at an initial infusion rate of 1 µg/kg/min. The use of bolus infusions of **REMIFENTANIL ADCO** during induction in cardiac surgical patients is not recommended. Endotracheal intubation should not occur until at least 5 minutes after the start of the infusion.

Maintenance period of anaesthesia:

After endotracheal intubation, the infusion rate of **REMIFENTANIL ADCO** should be titrated according to patient need. Supplemented 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 section **5.2 – Cardiac anaesthesia**).

Concomitant medication:

At the doses recommended above, **REMIFENTANIL ADCO** 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 remifentanil.

Continuation of post-operative analgesia prior to extubation:

It is recommended that the infusion of **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO**, patients must be given an alternative analgesic and sedative medicine at a sufficient time in advance. The choice and dose of medicines should be appropriate for the patient's level of post-operative care.

It is recommended that the **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** 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:

REMIFENTANIL ADCO 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 **REMIFENTANIL ADCO** is initiated at an infusion rate of 0,1 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 **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** 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:

DOSAGE GUIDELINES FOR USE OF REMIFENTANIL ADCO 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 **REMIFENTANIL ADCO** are not recommended in the intensive care setting. The use of **REMIFENTANIL ADCO** will reduce the dosage requirement of any concomitant sedative medicine 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.

Additional analgesia for ventilated patients undergoing stimulating procedures:

An increase in the existing **REMIFENTANIL ADCO** infusion rate may be required to provide additional analgesic cover for ventilated patients undergoing stimulating and/or painful procedures such as endotracheal suctioning, wound dressing and physiotherapy. It is recommended that a **REMIFENTANIL ADCO** 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 % - 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 REMIFENTANIL ADCO:

Due to the rapid offset of action of **REMIFENTANIL ADCO**, no residual opioid activity will be present within 5 to 10 minutes after discontinuation, regardless of the duration of infusion. Prior to discontinuation of **REMIFENTANIL ADCO**, 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 **REMIFENTANIL ADCO**.

Guidelines for extubation and discontinuation of REMIFENTANIL ADCO:

In order to ensure a smooth emergence from a **REMIFENTANIL ADCO**-based regimen, it is recommended that the infusion rate of **REMIFENTANIL ADCO** is titrated in stages to 0,1 µg/kg/min (6 µg/kg/h) over a period of up to 1 hour prior to extubation. Following extubation, the infusion rate should be reduced by 25 % decrements in at least 10-minute intervals until the infusion is discontinued. During weaning from the ventilator, the **REMIFENTANIL ADCO** infusion should not be increased and only down titration should occur, supplemented as required with alternative analgesics.

Upon discontinuation of **REMIFENTANIL ADCO**, 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.

SPECIAL PATIENT POPULATIONS:

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.

Elderly (over 65 years of age):

General anaesthesia:

The initial starting dose of remifentanil 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.

The 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 CARDIAC ANAESTHESIA – Dosage guidelines**).

Intensive care:

No initial dose reduction is required (see section **4.2 USE IN INTENSIVE CARE**).

Obese patients:

For obese patients (greater than 30 % over their ideal body weight) the dosage of **REMIFENTANIL ADCO** 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 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 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 **REMIFENTANIL ADCO** in this population. Initial dosage reduction and subsequent titration to effect is therefore recommended.

Cardiac anaesthesia:

No initial dose reduction is required (see section **4.2 CARDIAC ANAESTHESIA – Dosage guidelines**).

Long-term use in ICU:

No data are available on the long-term (longer than 24 hours) use of **REMIFENTANIL ADCO** in ICU patients.

Method of administration

Continuous infusion of **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** after use (see section 4.4).

REMIFENTANIL ADCO is for intravenous use only and must not be administered by epidural or intrathecal injection (see section 4.3).

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

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

Known hypersensitivity to any component of **REMIFENTANIL ADCO**, remifentanil and other fentanyl analogues.

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

REMIFENTANIL ADCO should not be used unless artificial ventilation is planned.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

REMIFENTANIL ADCO should be administered only by persons specifically trained in the use of anaesthetic medicines 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.

REMIFENTANIL ADCO should not be used in diagnostic or therapeutic procedures outside the monitored anaesthesia care setting. Patients receiving monitored anaesthesia care should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure. Oxygen saturation should be monitored on a continuous basis.

Resuscitative and intubation equipment, oxygen and an opioid antagonist must be readily available.

Inadvertent administration:

A sufficient amount of **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO**.

REMIFENTANIL ADCO may produce dependency.

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

Rapid offset of action:

Due to the rapid offset of action of **REMIFENTANIL ADCO** no residual opioid activity will be present within 5 to 10 minutes after discontinuation of **REMIFENTANIL ADCO**. For those patients undergoing surgical procedures where post-operative pain is anticipated, analgesics should be administered prior to, or immediately following discontinuation of **REMIFENTANIL ADCO**. 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 **REMIFENTANIL ADCO** 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 **REMIFENTANIL ADCO** as an analgesic may be treated by stopping or decreasing the rate of administration of **REMIFENTANIL ADCO**.

The effects of muscle rigidity on respiration may be more pronounced in patients with myasthenia gravis. Resolution of muscle rigidity after discontinuing the infusion of **REMIFENTANIL ADCO** occurs within minutes.

Respiratory depression – management:

Analgesia is accompanied by marked respiratory depression. Therefore, **REMIFENTANIL ADCO** 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 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 **REMIFENTANIL ADCO** 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.

4.5 Interactions with other medicines and other forms of interaction

REMIFENTANIL ADCO 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 such as alcohol, anaesthetics, anxiolytics, hypnotics and antipsychotics are not reduced, patients may experience an increased incidence of adverse effects associated with these medicines. The cardiovascular effects of **REMIFENTANIL ADCO** (hypotension and bradycardia), may be exacerbated in patients receiving

concomitant cardiac depressant medicines, such as beta-blockers and calcium channel blocking medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy and Lactation

Safety in pregnancy and lactation has not been established.

The safety profile of **REMIFENTANIL ADCO** during labour or delivery has not been demonstrated. There are insufficient data to recommend **REMIFENTANIL ADCO** for use during labour and caesarean section. **REMIFENTANIL ADCO** crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated summary of adverse reactions

Immune system disorders

Frequency unknown: Anaphylactic reactions.

Psychiatric disorders

Less frequent: Changes of mood, hallucinations.

Nervous System Disorders

Less frequent: Sedation (during recovery from general anaesthesia), headache, raised intracranial pressure, convulsions.

Eye disorders

Less frequent: Miosis.

Ear and labyrinth disorders

Less frequent: Vertigo.

Cardiac disorders

Frequent: Bradycardia.

Less frequent: Tachycardia, palpitations, deepening of coma, cardiac arrest/asystole usually preceded by bradycardia, has been reported in conjunction with other anaesthetic medicines.

Vascular disorders

Frequent: Hypotension, post-operative hypertension.

Less frequent: Orthostatic hypotension, circulatory failure.

Respiratory, thoracic and mediastinal disorders

Frequent: Acute respiratory depression, apnoea.

Less frequent: Hypoxia, pulmonary oedema, death may occur from respiratory failure.

Gastro-intestinal disorders

Frequent: Nausea, vomiting, constipation.

Less frequent: Abdominal discomfort, xerostomia, gastro-oesophageal reflux, dysphagia, diarrhoea, heartburn, ileus.

Skin and subcutaneous tissue disorders

Frequent: Pruritus.

Less frequent: Urticaria, contact dermatitis.

Frequency unknown: Rash, erythema and itching with transdermal use. Gum bleeding and irritation and taste perversion with transmucosal use. Facial flushing, hypothermia.

Musculoskeletal and connective tissue disorders

Frequent: Skeletal muscle rigidity.

Less frequent: Post-operative aches, restlessness.

Frequency unknown: Rhabdomyolysis progressing to renal failure.

Renal and urinary disorders

Less frequent: Micturition may be difficult and there may be ureteric or biliary spasm, antidiuretic effect.

Reproductive system and breast disorders

Less frequent: Decreased libido or potency.

General disorders and administration site conditions

Frequent: Post-operative shivering or aches, drowsiness, confusion.

Less frequent: Dry mouth, sweating, dizziness.

Frequency unknown: Pain and irritation at injection site.

Investigations

Less frequent: Alterations in liver enzyme values.

Social circumstances

Less frequent: Euphoric activity has led to abuse.

The following side effects were reported during post marketing spontaneous reports with the innovator molecule and are similar for **REMIFENTANIL ADCO** and applicable to **REMIFENTANIL ADCO**.

- Allergic reactions including anaphylaxis have been reported in patients receiving remifentanil in conjunction with one or more anaesthetic medicines.

- Cases of cardiac arrest, asystole usually preceded by bradycardia, have been reported in patients receiving remifentanil in conjunction with other anaesthetic medicines.

c. Description of selected adverse reactions

Not applicable

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Symptoms and signs:

Overdose would be manifested by an extension of the pharmacological actions of **REMIFENTANIL ADCO** i.e. respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. Due to the very short duration of action of **REMIFENTANIL ADCO**, 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 **REMIFENTANIL ADCO**;

- 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 **REMIFENTANIL ADCO** is unlikely to exceed the duration of action of the opioid antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; anaesthetics, Opioid anaesthetics,

ATC code: N01AH06

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

5.2 Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective half-life is 3 - 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 of which two-thirds is binding to alpha-1-acid-glycoprotein.

Metabolism:

Remifentanil is rapidly metabolised by hydrolysis of the propionic acid-methyl ester linkage by non-specific esterases in blood and tissue. The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite. 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 metabolised by plasma cholinesterase and is not appreciably metabolised by the liver or lung.

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 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 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 distributions 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 – 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 (approximately 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each vial contains 15 mg glycine and hydrochloric acid to buffer the solutions to a nominal pH of 3 after reconstitution.

6.2 Incompatibilities

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

REMIFENTANIL ADCO 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.

REMIFENTANIL ADCO should not be mixed with other therapeutic medicines prior to administration. This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Before reconstitution and dilution:

REMIFENTANIL 1 mg ADCO: 18 months

REMIFENTANIL 2 mg ADCO: 24 months

REMIFENTANIL 5 mg ADCO: 24 months

After reconstitution and dilution: The reconstituted solution is stable for 24 hours at or below 25 °C, however, from a microbiological consideration the medicine should preferably be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would

normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vial in the carton until required for use.

For single use only. Any unused solution should be discarded.

KEEP OUT OF REACH OF CHILDREN.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

REMIFENTANIL 1 mg ADCO: Each carton contains 5 vials of 3 ml each.

Each 3 ml colourless Type I glass vial has a grey chlorobutyl rubber stopper and a white polypropylene flip-off cap containing remifentanil hydrochloride (equivalent to 1 mg remifentanil base).

REMIFENTANIL 2 mg ADCO: Each carton contains 5 vials of 3 ml each.

Each 3 ml colourless Type I glass vial has a grey chlorobutyl rubber stopper and a green polypropylene flip-off cap containing remifentanil hydrochloride (equivalent to 2 mg remifentanil base).

REMIFENTANIL 5 mg ADCO: Each carton contains 5 vials of 6 ml each.

Each 6 ml colourless Type I glass vial has a grey chlorobutyl rubber stopper and a red polypropylene flip-off cap containing remifentanil hydrochloride (equivalent to 5 mg remifentanil base).

6.6 Special precautions for disposal and other handling

Reconstitution:

To reconstitute the powder, add 1 ml of IV fluid (**see IV fluids below**) per mg of remifentanil. Shake well to dissolve. **REMIFENTANIL ADCO** should be diluted to a final concentration of 20, 25, 50 or 250 µg/ml prior to administration.

50 µg/ml is the recommended dilution for adults and 20-25 µg/ml for paediatric patients aged 1 year and over. The dilution is dependent upon the technical capability of the infusion device and the expected requirements of the patient. **REMIFENTANIL ADCO** should not be administered without dilution.

Reconstitution and dilution of **REMIFENTANIL ADCO**:

Final concentration	Amount of **REMIFENTANIL ADCO** in each vial	Final volume after reconstitution and dilution
20 µg/ml	1 mg 2 mg 5 mg	50 ml 100 ml 250 ml
25 µg/ml	1 mg 2 mg 5 mg	40 ml 80 ml 200 ml
50 µg/ml	1 mg 2 mg 5 mg	20 ml 40 ml 100 ml
250 µg/ml	5 mg	20 ml

The reconstituted solution is stable for 24 hours at or below 25 ºC, however, from a microbiological consideration the product should preferably be used immediately. If not used immediately, in-use

storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

For single use only. Any unused solution should be discarded.

Further dilution to 20 to 250 µg/ml (50 µg/ml is the recommended dilution for adults and 20 – 25 µg/ml for paediatric patients aged 1 year and over) with one of the following IV fluids below:

- Sterilized Water for Injections
- 5 % Dextrose (glucose) Injection
- 5 % Dextrose (glucose) and 0,9 % Sodium Chloride Injection
- 0,9 % Sodium Chloride Injection
- 0,45 % Sodium Chloride Injection

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.

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8. REGISTRATION NUMBER(S)

REMIFENTANIL 1 mg ADCO: 45/2.9/1110

REMIFENTANIL 2 mg ADCO: 45/2.9/1111

REMIFENTANIL 5 mg ADCO: 45/2.9/1112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Date amended: 29 June 2022

PI 29 June 2022