S6 Rapifen® 2 ml IV injection

SCHEDULING STATUS
Schedule 6

PROPRIETARY NAME AND DOSAGE FORM
RAPIFEN® 2 ml IV injection

COMPOSITION
Each ml contains alfentanil hydrochloride 0,544 mg (equivalent to alfentanil base 0,5 mg) and sodium chloride 9,0 mg in water for injection.

PHARMACOLOGICAL CLASSIFICATION
A.2.7 Central nervous system depressants. Narcotic analgesics.

PHARMACOLOGICAL ACTION
Pharmacodynamics
Alfentanil is a narcotic analgesic with potent analgesic and respiratory depressant effects.

The onset of the action is rapid, the peak effect being reached within 1 minute. The duration of action is short, 11 minutes at twice and 17 minutes at four times the lowest ED_{50}.

At high doses (> 120 µg/kg), alfentanil induces sleep.

Recovery after alfentanil administration is rapid and smooth.

All actions of alfentanil are immediately and completely reversed by the specific narcotic antagonist naloxone hydrochloride.

Alfentanil maintains cardiovascular stability. It has not been shown to cause histamine release (in doses used clinically).

Pharmacokinetics
Alfentanil is rapidly eliminated after intravenous administration. Sequential distribution half-lives of 0,4 – 2,2 min and 8 – 32 min and terminal half-lives of 83 – 223 min have been reported. The low degree of ionisation (11 % at pH = 7,4) contributes to a rapid but limited tissue distribution. Reported volumes of distribution are 1,27 – 4,81 L (volume of distribution of the central compartment) and 12,1 – 98,2 L (volume of distribution at steady state). Plasma protein binding of Alfentanil is about 92 %. Alfentanil is mainly metabolised in the liver. Only 1 % of unchanged alfentanil is found in urine. Metabolites are inactive and 70 – 80 % of them are eliminated via the urine. The plasma clearance in young subjects averages 356 ml/min, and decreases with age.

Accumulation of alfentanil may occur under the following circumstances: With prolonged continuous infusion or with repeated administration of single doses and in patients with reduced plasma clearance e.g. patients with compromised liver function and patients over the age of 65 years.

Once steady state has been reached after infusion, the elimination half-life remains unaltered.

INDICATIONS
RAPIFEN is indicated for use as a narcotic analgesic in general anaesthesia for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures. It may also be used as an anaesthetic induction agent.

CONTRA-INDICATIONS
RAPIFEN is contra-indicated in patients with a known intolerance to the medicine or to opioids in general.

It should not be used in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have head injury or brain tumour.

Patients with a history of myasthenia gravis and myopathies.

WARNINGS
Bradycardia, and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic agents. Bradycardia can be treated with atropine.
Bradycardia may be more pronounced when alfentanil is combined with other anaesthetic agents, which depress the heart rate or increase vagal activity. Heart rate should therefore be monitored carefully.

As asystole has been reported, it is advisable to be prepared to administer an anticholinergic drug if the heart rate is considered low.

The use of rapid bolus injections of RAPIFEN should be avoided in patients with compromised intracerebral compliance, in such patients the transient decrease in the mean arterial pressure maybe accompanied by a reduction of cerebral perfusion pressure.

INTERACTIONS
Since MAO inhibitors have been reported to potentiate narcotic analgesics, the use of RAPIFEN in patients who have received MAO inhibitors within 2 weeks should be avoided.
When insufficient anticholinergic is administered or when RAPIFEN is given in combination with non-vagolytic muscle relaxants, bradycardia may occur.
Medicines such as barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective central nervous depressants (e.g. alcohol) may potentiate the respiratory depression of RAPIFEN. When patients have received such medicines, the dose of RAPIFEN required will be less than usual.
Likewise, following the administration of RAPIFEN, the dose of the other central nervous system depressant drugs should be reduced.

RAPIFEN is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of RAPIFEN is inhibited by fluconazole, voriconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors*).*
In-vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may also inhibit the metabolism of RAPIFEN. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of RAPIFEN.
Effect of RAPIFEN on the metabolism of other medicines: In combination with RAPIFEN, the blood concentrations of propofol are 17 % higher than in the absence of RAPIFEN. The concomitant use of RAPIFEN and propofol may require a lower dose of RAPIFEN.

PREGNANCY AND LACTATION
The safe use of RAPIFEN in pregnancy has not been established.

Administration (IM or IV) during childbirth (including caesarian section) is not recommended, because RAPIFEN crosses the placenta and because the fetal respiratory centre is more sensitive to opiates. Nevertheless, if RAPIFEN is administered, an antidote for the child should always be at hand.

RAPIFEN may enter the maternal milk. Therefore nursing is not recommended during 24 hours following the administration of RAPIFEN.

DOSAGE AND DIRECTIONS FOR USE

WARNING: Must only be administered when adequate facilities for the use of ventilators and muscle relaxants are close at hand.

The dosage should be individualised. Some of the factors to be considered in determining the dose are age, body mass, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used and type and duration of the surgical procedure.

The initial dose should be reduced in the elderly and debilitated patients. In children it should be increased. The effect of the initial dose should be taken into account in determining supplemental doses. To avoid bradycardia, it is recommended to administer a small intravenous dose of an anticholinergic just before induction.

For short procedures and use in outpatients:
RAPIFEN in small doses is useful for minor, short but painful surgical procedures and for outpatients, provided good monitoring equipment is available in the operating room.

A bolus dose of 7 - 15 µg/kg given intravenously should be adequate for procedures lasting less than 10 minutes. If this dose is injected slowly, respiration may be maintained at a decreased level. Should the duration of the procedure exceed 10 minutes, further increments of 7 - 15 µg/kg should be given every 10 - 15 minutes or as required.

Outpatients: An anticholinergic, a short-acting induction agent (e.g. RAPIFEN) and $N_20/0_2$ are recommended.

For procedures of medium duration:

WARNING: Respiration will be depressed and ventilation will be required.

The dose of the initial intravenous bolus should be adapted to the expected duration of the surgical procedure as follows:

Duration of the procedure (minutes)	RAPIFEN (0,5 mg/ml) IV bolus dose	
	(µg/kg)	ml per 70 kg
10 – 30	20 – 40	3 – 6
30 – 60	40 – 80	6 – 12
> 60	80 – 150	12 – 20

When surgery is more prolonged or aggressive, analgesia should be maintained by:
- increments of 15 µg/kg of RAPIFEN when required (to avoid post-operative respiratory depression, the last dose of RAPIFEN should not be administered within the last 10 minutes of surgery).
  or
- RAPIFEN infusion at a rate of 1 µg/kg/min (0,14 ml of RAPIFEN 0,5 mg/ml per 70 kg/min) until 5 - 10 minutes before the end of surgery.

Periods of very painful stimuli can easily be overcome by small increments of RAPIFEN or by temporarily increasing the infusion rate.

When using RAPIFEN without $N_20/0_2$ or other inhalation anaesthetic agents, the maintenance dose of RAPIFEN should be increased.

For long procedures:

WARNING: Respiration will be depressed and ventilation will be required.

RAPIFEN may be used as the analgesic component of anaesthesia for surgical procedures of long duration especially when rapid extubation is indicated. Optimum analgesia and a stable autonomic condition are maintained by means of an individually adapted initial intravenous dose and by varying the infusion rate according to the surgical stimuli and the clinical reactions of the patient.

Induction:

WARNING: Respiration will be depressed and ventilation will be required.

An intravenous bolus dose of ≥ 120 µg/kg (17 ml of RAPIFEN 0,5 mg/ml per 70 kg) RAPIFEN will induce hypnosis and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Adverse reactions:

The most common adverse reaction that may occur with RAPIFEN is respiratory depression. This reaction is more likely when the intravenous dosage is given too rapidly. Should respiratory depression occur during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia.

Respiratory depression and analgesia, which may persist into or recur in the post-operative period, can be immediately and completely reversed by the specific narcotic antagonist, naloxone hydrochloride.
Because the duration of respiratory depression may exceed the duration of action of the antagonist, the patient should be monitored closely and repeated treatment with the antagonist may be indicated.

RAPIFEN may induce myoclonic movements and muscle rigidity, particularly of the chest wall during induction.
Rigidity may be avoided by the following measures:
- Slow intravenous injection: this should be adequate for lower doses of RAPIFEN.
- Benzodiazepine premedication: should reduce muscle rigidity.
- Muscle relaxants, at full paralysing dose, administered just prior to RAPIFEN should completely eliminate muscle rigidity.

Nausea and vomiting can be controlled with anti-emetics.

Clinical Trial Data
The safety of RAPIFEN was evaluated in 1 157 subjects who participated in 18 clinical trials. Adverse Drug Reactions that were reported for ≥ 1% of -RAPIFEN-treated subjects in these trials are shown in Table 1.
Table 1: Adverse Reactions that were reported for ≥ 1% of RAPIFEN-treated subjects in 18 Clinical Trials.

System Organ Class Adverse Reactions	RAPIFEN (n=1 157)/%
Psychiatric disorders	
Euphoric mood	1,8
Nervous System disorders	
Movement disorders	7,9
Dizziness	2,4
Sedation	1,5
Dyskinesia	1.4
Eye disorder	
Visual disturbance	1,1
Cardiac Disorders	
Bradycardia	5,4
Tachycardia	1,0
Vascular disorders	
Hypotension	4,1
Hypertension	2,2
Blood pressure decreased	1,3
Blood pressure increased	1,0
Respiratory, thoracic and mediastinal disorders	
Apnoea	8,6
Gastrointestinal disorders	
Nausea	17,0
Vomiting	14,0
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity	3,1
General disorders and administration site conditions	
Fatigue	2,0
Chills	1,8
Injection site pain	1,6
Injury, poisoning, and procedural Complications	
Procedural pain	1,1

Additional Adverse Reactions that occurred in < 1 % of RAPIFEN-treated subjects in the 18 clinical trial are listed below in Table 2.

Table 2: Adverse Reactions that occurred in < 1 % of RAPIFEN-treated subjects in18 clinical trials of RAPIFEN

System. Organ class Adverse Reaction
Psychiatric disorders
Agitation
Crying
Nervous System disorders
Headache
Somnolence
Unresponsive to stimuli
Cardiac Disorders
Arrhythmia
Heart rate decreased
Vascular disorders
Vein pain
Respiratory, thoracic and mediastinal disorders
Bronchospasm
Hiccups
Hypercapnia
Laryngospasm
Epistaxis
Respiratory depression
Skin and Subcutaneous Tissue Disorder
Dermatitis allergic
Hyperhidrosis
Pruritus
General disorders and administration site conditions
Pain
Injury, poisoning, and procedural Complications
Confusion postoperative
Agitation postoperative
Airway complications of anaesthesia
Anaesthetic complication neurological
Procedural complication
Endotracheal intubation complication

Postmarketing Data
Adverse reactions from spontaneous reports during the postmarketing experience with RAPIFEN are included in Table 3.

Table 3. Postmarketing reports of adverse reactions estimated from spontaneous reporting rates

Immune system disorders
Hypersensitivity (including anaphylactic reactions, anaphylactoid reactions, and urticaria)
Psychiatric disorders
Disorientation
Nervous system disorders
Loss of consciousness (Postoperative period), Convulsion, Myoclonus,
Eye disorders
Miosis
Cardiac disorders
Cardiac arrest
Vascular disorders
Hypotension, Hypertension
Respiratory, thoracic and mediastinal disorders
Respiratory arrest, Respiratory depression (including fatal outcome), Cough
Skin and subcutaneous tissue disorders
Erythema, rash
General disorders and administration site conditions
Pyrexia

Special Precautions:
Patients who have received RAPIFEN should remain under appropriate surveillance.

Resuscitation equipment and a narcotic antagonist should be available to manage apnoea. The duration of respiratory depression is dose-related, but short and is immediately reversed by the specific narcotic antagonist, naloxone hydrochloride.

Because of its weak cholinergic activity, RAPIFEN should be used with caution in patients with cardiac arrhythmias.

Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

Hyperventilation during anaesthesia may alter the patient's response to CO_2, thus affecting respiration postoperatively.

RAPIFEN may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

It is recommended to reduce the dosage in the elderly or debilitated patients. RAPIFEN should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease; decreased respiratory reserve; alcoholism; impaired hepatic or renal function. Such patients also require prolonged postoperative monitoring.

Effects on driving ability and use of machinery:
Car driving and the operation of machinery can only be resumed when sufficient time has elapsed after administration of RAPIFEN. Individual reactions vary greatly. On average, the patient should wait 6 hours after doses of 1 to 3 ml and 24 hours after higher doses and infusions.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Symptoms:
The manifestations of RAPIFEN overdosage are an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture will be determined primarily by respiratory depression, varying from bradypnoea to apnoea.

Treatment:
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. Endotracheal intubation will be necessary for the administration of oxygen in apnoea. The specific narcotic antagonist (naloxone hydrochloride) should be available for use as indicated to manage respiratory depression. The adult dose of naloxone hydrochloride is 0,4 mg intravenously and in children the dosage is 0,01 mg/kg body mass, repeated at 2 - 3 minute intervals until sufficient reversal is obtained. This does not preclude the use of more immediate countermeasures.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed; body warmth and adequate fluid intake should be maintained.

If hypotension occurs and is severe or persists, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

IDENTIFICATION
A clear colourless solution in 2 ml glass ampoules free from visible foreign matter.

PRESENTATION
Cartons containing 5 x 2 ml ampoules.

STORAGE INSTRUCTIONS
Store below 25 °C. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
2 ml: Q/2.7/327.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Piramal Critical Care

Piramal Critical Care South Africa (Pty) Ltd,
Office 2, Ground Floor, Kiepersol House,
300 Acacia Road, Darrenwood, 2194

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S6 Rapifen® 2 ml IV inspuiting

SKEDULERINGSTATUS
Skedule 6

EIENDOMSNAAM EN DOSEERVORM
RAPIFEN 2 ml IV inspuiting

SAMESTELLING
Elke ml bevat alfentanielhidrochloried 0,544 mg (ekwivalent aan alfentaniel-basis 0,5 mg) en natriumchloried 9,0 mg in water vir inspuiting.

FARMAKOLOGIESE KLASSIFIKASIE
A.2.7 Sentrale senuweestelsel depressante. Narkotiese analgetika.

FARMAKOLOGIESE WERKING
Farmakodinamika
Alfentaniel is 'n narkotiese pynstiller met kragtige pynstillende effekte, asook 'n sterk onderdrukkende effek op die asemhalingstelsel.

Die aanvangs van werking is vinnig, met 'n piekeffek wat binne 1 minuut bereik word. Die duurte van werking is kort, 11 minute teen tweekeer en 17 minute teen vier keer die laagste ED_{50}.

Teen hoër dosisse (> 120 µg/kg) induseer alfentaniel slaap.

Herstel na die toediening van alfentaniel is vinnig en geleidelik.

Al die aksies van alfentaniel word onmiddellik en volledig deur die spesifieke narkotiese antagonis, naloksoonhidrochloried, omgekeer.

Alfentaniel onderhou kardiovaskulêre stabiliteit. Daar is aangetoon dat dit nie die vrystelling van histamien veroorsaak nie (in klinies gebruikte dosisse).

Farmakokinetika
Alfentaniel word vinnig na intraveneuse toediening geëlimineer, Opvolgende verspreidingshalfleeftye van 0,4 – 2,2 minute en 8 – 32 minute, en terminale halfleeftye van 83 – 223 minute is aangemeld. Die lae graad van ionisering (11 % teen pH = 7,4) dra by tot 'n vinnige dog beperkte weefselverspreiding. Aangemelde verspreidingsvolumes is 1,27 – 4,8 L (verspreidingsvolume van die sentrale kompartement) en 12,1 – 98,2 L (verspreidingsvolume teen stabiele staat). Die plasmaproteïenbinding van alfentaniel is ongeveer 92 %. Alfentaniel word hoofsaaklik deur die lewer gemetaboliseer. Slegs 1 % van onveranderde alfentaniel word in die uriene gevind. Die metaboliete is onaktief en 70 – 80 % van hulle word in die uriene uitgeskei. Die plasmasuiwering in jong persone is gemiddeld 356 ml/min, en verminder met ouderdom.

Akkumulasie van alfentaniel mag onder die volgende omstandighede voorkom: met verlengde, aanhoudende infusie of met die herhaaldelike toediening van enkel dosisse, asook in pasiënte met verminderde plasmasuiwering bv. pasiente met beperkte lewerfunksie en pasiënte ouer as 65 jaar.

Wanneer die stabiele staat na infusie bereik word, bly die eliminasiehalfleeftyd onveranderd.

INDIKASIES
RAPIFEN word aangedui vir gebruik as 'n narkotiese pynstiller in algemene narkose vir beide kort (bolusinspuitings) en lang (bolus, aangevul met inkremente of per infusie) chirurgiese prosedures. Dit mag ook as 'n induksiemiddel vir narkose gebruik word.

KONTRA-INDIKASIES
RAPIFEN word teenaangedui in pasiënte met 'n intoleransie teen die medisyne of teen opioïede in die algemeen.

Dit behoort nie gebruik te word in pasiënte wat veral vatbaar vir respiratoriese onderdrukking is nie, soos bv. bewustelose pasiënte wat moontlik aan 'n kopbesering of breintumor ly.

Pasiënte met 'n geskiedenis van miastenie gravis of miopatieë.

WAARSKUWINGS
Bradikardie en moontlik hartstilstand, kan voorkom as die pasiënt nie voldoende anticholinergika ontvang het nie. Bradikardie kan met atropien behandel word. Bradikardie mag meer uitgesproke wees wanneer alfentaniel met ander narkotiese middels wat die harttempo onderdruk of vagusaktiwiteit verhoog, gebruik word. Die harttempo behoort daarom noukeurig gemonitor te word.

Aangesien asistolie aangemeld is, is dit raadsaam om daarop voorbereid te wees om 'n anticholinergiese middel toe te dien indien die harttempo as laag beskou word.

Die gebruik van vinnige bolusinspuitings van RAPIFEN behoort vermy te word in pasiënte met beperkte intra-serebrale inskiklikheid. In sulke pasiënte mag die verbygaande afname in gemiddelde arteriële druk met 'n afname in serebrale perfusiedruk gepaardgaan.

INTERAKSIES
Aangesien dit aangemeld is dat MAO-inhibeerders narkotiese pynstillers potensieer, behoort die gebruik van RAPIFEN in pasiënte wat MAO-inhibeerders binne twee weke van tevore gebruik het, vermy te word.

Wanneer onvoldoende anticholinergiese middels toegedien word of wanneer RAPIFEN in kombinasie met nie-vagolitiese spierverslappers gebruik word, mag bradikardie voorkom.

Medisyne soos barbiturate, bensodiasepiene, neuroleptika, halogeengasse en ander nie-selektiewe sentrale senuweestelselonderdrukkers (bv. alkohol) mag die respiratoriese onderdrukking van RAPIFEN potensieer. Wanneer pasiënte sulke medisyne ontvang het, sal die dosis RAPIFEN wat benodig word, minder as gewoonlik wees. Eweneens behoort die dosis van ander sentrale senuweestelselonderdrukkende middels na die toediening van RAPIFEN verminder te word.

RAPIFEN word hoofsaaklik deur die menslike sitochroom P450 3A4 ensiem gemetaboliseer. Beskikbare menslike farmakokinetiese data dui daarop dat die metabolisme van RAPIFEN deur flukonasool, vorikonasool, eritromisien, diltiasem en simetidien (bekende sitochroom P450 3A4 ensieminhibeerders) geïnhibeer word. *In vitro* data wil daarop dui dat ander kragtige sitochroom P450 3A4 ensieminhibeerders (bv. ketokonasool, itrakonasool, ritonavir) ook die metabolisme van RAPIFEN mag inhibeer. Dit kan die risiko van verlengde of vertraagde asemhalingsonderdrukking verhoog. Die gelyktydige gebruik van sulke middels vereis spesiale pasiëntesorg en –observasie; dit mag veral nodig wees om die RAPIFEN dosis te verminder.

Effek van RAPIFEN op die metabolisme van ander medisynes: Die bloedkonsentrasie van propofol is 17 % hoër in kombinasie met RAPIFEN, as wat dit in die afwesigheid van RAPIFEN is. Die gesamentlike gebruik van RAPIFEN en propofol kan 'n laer dosis RAPIFEN benodig.

SWANGERSKAP EN LAKTASIE
Die veilige gebruik van RAPIFEN gedurende swangerskap is nie vasgestel nie.

Die toediening (IM of IV) gedurende die geboorteproses (insluitende 'n keisersnit) word nie aanbeveel nie, aangesien RAPIFEN deur die plasenta beweeg en ook aangesien die fetale respiratoriese sentrum meer sensitief teen opiate is. Indien RAPIFEN egter wel toegedien word, behoort 'n teenmiddel vir die kind altyd byderhand te wees. RAPIFEN mag in moedersmelk voorkom. Daarom word borsvoeding nie vir 24 uur na die toediening van RAPIFEN aanbeveel nie.

DOSIS EN GEBRUIKSAANWYSINGS

WAARSKUWING: Moet slegs toegedien word wanneer voldoende fasiliteite vir die gebruik van ventilators en spierverslappers byderhand is.

Die dosis behoort geïndividualiseer te word. Sommige van die faktore wat in die bepaling van die dosis oorweeg behoort te word is ouderdom, liggaamsmassa, fisiese kondisie, onderliggende patologiese kondisie, die gebruik van ander medisyne, tipe van narkose wat gebruik gaan word en die tipe en duurte van die chirurgiese prosedure.

Die aanvanklike dosis behoort in bejaardes en verswakte pasiënte verminder te word. In kinders behoort dit verhoog te word. Die effek van die aanvanklike dosis moet in gedagte gehou word wanneer aanvullende dosisse bereken word. Om bradikardie te voorkom word dit aanbeveel dat 'n klein hoeveelheid van 'n intraveneuse anticholinergiese middel kort voor induksie toegedien word.

Vir kort prosedures en gebruik in buite-pasiënte:
RAPIFEN in klein dosisse is nuttig vir klein, kort maar pynlike chirurgiese prosedures en vir buite-pasiënte, op voorwaarde dat daar goeie moniteringstoerusting in die operasiekamer is.

'n Bolusdosis van 7 – 15 µg/kg intraveneus toegedien behoort voldoende te wees vir prosedures wat korter as 10 minute duur. As die dosis stadig toegedien word kan asemhaling teen 'n laer vlak onderhou word. Indien die duurte van die prosedure langer as 10 minute is, behoort verdere inkremente van 7 – 15 µg/kg elke 10 tot 15 minute of soos benodig, toegedien te word.

Buite-pasiënte: 'n Anticholinergiese middel, 'n kortwerkende induksiemiddel (bv. RAPIFEN) en $N_20/0_2$ word aanbeveel.

Vir prosedures met 'n medium duurte:

WAARSKUWING: Asemhaling sal onderdruk word en ventilering word benodig.

Die dosis van die aanvanklike bolus behoort as volg by die verwagte duurte van die prosedure aangepas te word:

Duurte van die prosedure (minute)	RAPIFEN (0,5 mg/ml) IV bolusdosis	
	(µg/kg)	ml per 70 kg
10 – 30	20 – 40	3 – 6
30 – 60	40 – 80	6 – 12
> 60	80 – 150	12 – 20

Wanneer chirurgie langer of meer aggressief is, behoort narkose onderhou te word met:
- inkremente van 15 µg/kg RAPIFEN wanneer nodig (om post-operatiewe respiratoriese onderdrukking te vermy, behoort die laaste RAPIFEN dosis nie binne die laaste 10 minute van chirurgie toegedien te word nie)
  of
- RAPIFEN infusie teen 'n tempo van 1 µg/kg/min (0,14 ml RAPIFEN 0,5 mg/ml per 70 kg/min) tot 5 – 10 minute voor die einde van chirurgie

Periodes van baie pynlike stimuli kan baie maklik oorkom word met klein inkremente van RAPIFEN of deur die infusietempo tydelik te versnel.

Wanneer RAPIFEN sonder $N_20/0_2$ of ander ingeademde narkosemiddels gebruik word, behoort die onderhoudsdosis van RAPIFEN verhoog te word.

Vir lang prosedures:

WAARSKUWING: Asemhaling sal onderdruk word en ventilasie sal benodig word.

RAPIFEN kan as die pynverligtende komponent van narkose vir chirurgiese prosedures van lang duurte gebruik word, veral wanneer vinnige ekstubering aangedui word. Optimum pynverligting en 'n stabiele outonomiese kondisie word deur middel van 'n indiwidueel aangepaste aanvanklike intraveneuse dosis onderhou, asook deur aanpassing van die infusietempo volgens die chirurgiese stimuli en kliniese reaksies van die pasiënt.

Induksie:

WAARSKUWING: Asemhaling sal onderdruk word en ventilasie sal benodig word.

'n Intraveneuse bolus van ≥ 120 µg/kg (17 ml RAPIFEN 0,5 mg/ml per 70 kg) RAPIFEN sal hipnose en pynverligting induseer, terwyl goeie kardiovaskulêre stabiliteit in pasiënte met voldoende spierverslapping onderhou sal word.

NEWE-EFFEKTE EN SPESIALE VOORSORGSMAATREËLS
Newe-effekte:

Die mees algemene newe-effek wat met RAPIFEN mag voorkom is respiratoriese onderdrukking. Hierdie reaksie sal meer waarskynlik voorkom wanneer die intraveneuse dosis te vinnig toegedien word. Indien respiratoriese onderdrukking gedurende narkose sou voorkom, sal ondersteunende of gekontroleerde respirasie voldoende ventilasie verskaf sonder dat die pynverdowing omgekeer word.

Respiratoriese onderdrukking en pynverdowing wat in die post-operatiewe periode mag aanhou of weer voorkom, kan onmiddellik en volledig met die spesifieke narkotiese antagonis, naloksoonhidrochloried, omgekeer word. Aangesien die duurte van respiratoriese onderdrukking die duurte van die werking van die antagonis mag oorskry, behoort die pasiënt noukeurig gemonitor te word en herhaalde behandeling met die antagonis mag aangedui word.

RAPIFEN mag miokloniese bewegings en spierstyfheid induseer, veral van die borswand tydens induksie.

Styfheid kan met die volgende maatreëls vermy word:
- Stadige intraveneuse inspuiting: dit behoort voldoende vir lae dosisse van RAPIFEN te wees
- Bensodiasepien premedikasie: behoort spierstyfheid te verminder
- Spierverslappers, teen die volle paraliserende dosis, toegedien kort voor RAPIFEN, behoort spierstyfheid volledig te elimineer.

Naarheid en braking kan met anti-emetiese middels beheer word.

Kliniese proewe data
Die veiligheid van RAPIFEN is onder 1 157 proefpersone geëvalueer wat aan 18 kliniese proewe deelgeneem het. Die ongunstige reaksies wat by ≥ 1% RAPIFEN-behandelde proefpersone aangemeld is tydens hierdie proewe, word in Tabel 1 weergegee.

Tabel 1: Ongunstige reaksies aangemeld by ≥ 1% RAPIFEN-behandelde proefpersone in 18 kliniese proewe:

Sisteem-orgaanklas ongunstige reaksies	RAPIFEN ('n=1 157) / %
Psigiatriese afwykings	
Euforiese gemoedstoestand	1,8
Senuweestelsel afwykings	
Bewegingsiekte	7,9
Duiseligheid	2,4
Sedasie	1,5
Diskinesie	1,4
Oogsiektes	
Visuele versteuring	1,1
Kardiale afwykings	
Bradikardie	5,4
Tagikardie	1,0
Vaskulêre afwykings	
Hipotensie	4,1
Hipertensie	2,2
Bloeddruk verlaag	1,3
Bloeddruk verhoog	1,0
Respiratoriese, bors- en mediastinum afwykings	
Apnee	8,6
Gastroïntestinale afwykings	
Naarheid	17,0
Braking	14,0
Skeletspierstelsel- en bindweefsel afwykings	
Spierstyfheid	3,1
Algemene siektes en toestande by die plek van toediening	
Moegheid	2,0
Koue rillings	1,8
Pyn by plek van inspuiting	1,6
Besering, vergiftiging en komplikasie met prosedure	
Pyn met prosedure	1,1

Bykomende newe-effekte wat by < 1 % RAPIFEN-behandelde proefpersone in die 18 kliniese proewe voorgekom het, word in Tabel 2 gelys.

Tabel 2: Newe-effekte wat by < 1 % RAPIFEN-behandelde proefpersone in 18 kliniese proewe met RAPIFEN voorgekom het:

Sisteem-orgaanklas Ongunstige reaksie
Psigiatriese afwykings
Opgewondenheid
Huilerigheid
Senuweestelsel afwykings
Hoofpyn
Lomerigheid
Reageer nie op prikkels nie
Kardiale afwykings
Aritmieë
Afname in harttempo
Vaskulêre afwykings
Pynlike are
Respiratoriese-, bors- en mediastinum afwykings
Brongospasma
Hik
Hiperkapnie
Laringospasma
Epistakse
Respiratoriese onderdrukking
Vel- en onderhuidse weefsel afwykings
Allergiese dermatitis
Hiperhidrose
Pruritus
Algemene siektes en toestande by die plek van toediening
Pyn
Besering, vergiftiging en komplikasies met prosedure
Post-operatiewe verwarring
Post-operatiewe opgewondenheid
Lugwegkomplikasies van narkose
Neurologiese komplikasie van narkose
Komplikasie met prosedure
Komplikasie met endotrageale intubering

Na-bemarkings data:
Die spontane ongunstige reaksies wat in assosiasie met RAPIFEN tydens na-bemarkingsondervinding aangemeld is, word in Tabel 3 hieronder ingesluit.

TABEL 3. Na-bemarkingsberigte van ongunstige reaksies, beraam uit spontane aanmeldingskoerse

Immuunsisteemafwykings:
Hipersensitiwiteit (insluitende anafilaktiese reaksies, anafilaktoïede reaksies en urtikaria)
Psigiatriese afwykings:
Disoriëntasie.
Afwykings van die senuweestelsel;
Verlies van bewussyn (post-operatiewe periode), konvulsies, mioklonus.
Gesigsafwykings:
Miose.
Hartafwykings:
Hartstilstand.
Vaskulêre afwykings:
Hipotensie; Hipertensie
Asemhalingstelsel, torakale en mediastinale afwykings:
Respiratoriese arres, respiratoriese onderdrukking (insluitende die dood), hoes.
Afwykings van die vel en –aanhangsels:
Eriteem, uitslag.
Algemene afwykings en afwykings by die plek van aanwending:
Pireksie.

Spesiale voorsorgsmaatreëls:
Pasiënte wat RAPIFEN ontvang het behoort onder die nodige observasie gehou te word.

Resussiteringstoerusting en 'n narkotiese antagonis behoort byderhand te wees om apnee te bestuur. Die duurte van respiratoriese onderdrukking is dosisverwant, maar kort en word onmiddellik met die spesifieke narkotiese antagonis, naloksoonhidrochloried, omgekeer.

Weens sy swak cholinergiese aktiwiteit behoort RAPIFEN met sorg in pasiënte met hartarritmieë gebruik te word.

Pasiënte op chroniese opioïedterapie of pasiënte met 'n geskiedenis van opioïedmisbruik mag hoër dosisse vereis.

Hiperventilering gedurende narkose mag die pasiënt se respons tot CO_2 verander, wat die post-operatiewe asemhaling mag beïnvloed.

RAPIFEN mag hipotensie induseer, veral in hipovolemiese pasiënte. Die nodige maatreëls om 'n stabiele arteriële druk te onderhou behoort getref te word.

Dit word aanbeveel dat die dosis in bejaarde en verswakte pasiënte verminder word. RAPIFEN moet met sorg in pasiënte met enige van die volgende kondisies getitreer word: onbeheerde hipotiroïedisme; longsiekte; verlaagde respiratoriese reserwe; alkoholisme; belemmerde lewer- of nierfunksie. Sulke pasiënte vereis ook langer post-operatiewe monitering.

Effek op die vermoë om te bestuur of om met masjinerie te werk:
Die bestuur van 'n motor en die gebruik van masjinerie kan slegs hervat word wanneer voldoende tyd na die toediening van RAPIFEN verloop het. Indiwiduele reaksies wissel tot 'n groot mate. Oor die algemeen behoort die pasiënt vir 6 ure na 'n dosis van 1 tot 3 ml en 24 uur na hoër dosisse en infusies te wag.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN

Simptome:
Die manifestasies van oordosering met RAPIFEN is 'n verlenging van sy farmakologiese werking. Afhangende van die indiwiduele sensitiwiteit sal die kliniese prentjie primêr deur respiratoriese onderdrukking, wat wissel van bradipnee tot apnee, bepaal word.

Behandeling:
In die teenwoordigheid van hipoventilasie of apnee, behoort suurstof toegedien te word en behoort asemhaling ondersteun of beheer te word soos aangedui. Endotracheale intubering sal nodig wees vir die toediening van suurstof in apnee. Die spesifieke narkotiese antagonis (naloksoon-hidrochloried) behoort soos aangedui byderhand te wees om respiratoriese onderdrukking te bestuur. Die volwasse dosis van naloksoonhidrochloried is 0,4 mg intraveneus toegedien, terwyl die dosis 0,01 mg/kg liggaamsmassa in kinders is, herhaal met 2 – 3 minute tussenposes totdat voldoende omkering verkry is. Dit sluit nie die gebruik van meer onmiddellike teenmaatreëls uit nie.

Indien respiratoriese onderdrukking met spierstyfheid gepaardgaan, mag 'n intraveneuse neuromuskulêre blokkerende middel moontlik nodig wees om ondersteunde of gekontroleerde asemhaling te vergemaklik. Die pasiënt behoort sorgvuldig onder observasie gehou te word; liggaamstemperatuur en voldoende vloeistofinname behoort onderhou te word.

Indien hipotensie voorkom en erg is of aanhou, behoort die moontlikheid van hipovolemie oorweeg en met toepaslike parenterale vloeistofterapie bestuur te word.

IDENTIFIKASIE
'n Helder, kleurlose oplossing in 2 ml glasampules, vry van enige sigbare vreemde materiaal.

AANBIEDING
Kartonhouers met 5 X 2 ml ampules.

BERGINGSINSTRUKSIES
Bewaar benede 25°C. Beskerm teen lig.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS
2 ml: Q/2.7/327

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

Piramal Critical Care

Piramal Critical Care South Africa (Pty) Ltd,
Office 2, Ground Floor, Kiepersol House,
300 Acacia Road, Darrenwood, 2194

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