SCHEDULING STATUS

Schedule 6

PROPRIETARY NAME AND DOSAGE FORM

RAPIFEN® 2 ml IV injection

RAPIFEN® 10 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 ED50.

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

Shaded areas=NOT MARKETED
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 N₂O/O₂ are recommended.

**For procedures of medium duration:**

<table>
<thead>
<tr>
<th>Duration of the procedure (minutes)</th>
<th>RAPIFEN (0.5 mg/ml) IV bolus dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(µg/kg)</td>
</tr>
<tr>
<td>10 - 30</td>
<td>20 - 40</td>
</tr>
<tr>
<td>30 - 60</td>
<td>40 - 80</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>80 - 150</td>
</tr>
</tbody>
</table>

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

Shaded areas=NOT MARKETED
- 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 N₂O/O₂ 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 1157 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 Drug Reactions that were reported for ≥ 1% of RAPIFEN-treated subjects in 18 Clinical Trials.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Event</th>
<th>RAPIFEN (n=1157)/%</th>
</tr>
</thead>
</table>

Shaded areas=NOT MARKETED  24/2/09
<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Euphoric mood</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Nervous System disorders</strong></td>
<td>Movement disorders</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Eye disorder</strong></td>
<td>Visual disturbance</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Bradycardia</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypotension</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Blood pressure decreased</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Blood pressure increased</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Apnoea</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14.0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Muscle rigidity</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Injection site pain</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Injury, poisoning, and procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Shaded areas=NOT MARKETED 24/2/09
Additional Adverse Drug Reactions that occurred in <1% of RAPIFEN-treated subjects in the 18 clinical trial are listed below in Table 2.

Table 2: Adverse Drug Reactions that occurred in <1% of RAPIFEN-treated subjects in 18 clinical trials of RAPIFEN

<table>
<thead>
<tr>
<th>System.Organ class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Crying</td>
</tr>
<tr>
<td><strong>Nervous System disorders</strong></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Unresponsive to stimuli</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Heart rate decreased</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Vein pain</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Hiccups</td>
</tr>
</tbody>
</table>
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 drug reactions from spontaneous reports during the postmarketing experience with RAPIFEN are included in Table 3.
Table 3. Postmarketing reports of adverse drug 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.

Shaded areas=NOT MARKETED  24/2/09
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 CO₂, 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 or 10 ml glass ampoules free from visible foreign matter.

PRESENTATION
Cartons containing 5 x 2 ml and 5 x 10 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.
10 ml: Q/2.7/328.

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

JANSSEN PHARMACEUTICA (Pty.) Ltd.
(Reg No.: 1980/011122/07)
Building 6, Country Club Estate,
21 Woodlands Drive, Woodmead, 2191
Tel: +27 (11) 518 7000

Shaded areas=NOT MARKETED  24/2/09
DATE OF PUBLICATION OF THE PACKAGE INSERT

February 2010