1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 2.5 mg oromucosal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled oral syringe contains 2.5 mg midazolam (as hydrochloride) in 0.5 ml solution

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oromucosal solution
Clear colourless solution
pH 2.9 to 3.7

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy

For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. See section 4.2

4.2 Posology and method of administration

Posology

Standard doses are indicated below:

<table>
<thead>
<tr>
<th>Age range</th>
<th>Dose</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 6 months hospital setting</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>&gt; 6 months to &lt; 1 year</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>1 year to &lt; 5 years</td>
<td>5 mg</td>
<td>Blue</td>
</tr>
<tr>
<td>5 years to &lt; 10 years</td>
<td>7.5 mg</td>
<td>Purple</td>
</tr>
<tr>
<td>10 years to &lt; 18 years</td>
<td>10 mg</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought and the empty syringe given to the healthcare professional to provide information on the dose received by the patient.
A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice (see section 5.2).

Special populations

Paediatric population
The safety and efficacy of midazolam in children aged 0 to 3 months has not been established. No data are available.

Renal impairment
No dose adjustment is required, however, BUCCOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged. (see section 4.4)

Hepatic impairment
Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment (see section 4.4). BUCCOLAM is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration
BUCCOLAM is for oromucosal use. The full amount of solution should be inserted slowly into the space between the gum and the cheek. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

Precautions to be taken before manipulating or administering the product
No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe. BUCCOLAM is not for intravenous use. The oral syringe cap should be removed before use to avoid risk of choking.

4.3 Contraindications

Hypersensitivity to the active substance, benzodiazepines or to any of the excipients.
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic impairment

4.4 Special warnings and precautions for use

Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of BUCCOLAM in the 3-6 month age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.
Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

4.5 Interaction with other medicinal products and other forms of interaction

Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, a careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Anaesthetics and narcotic analgesics: Fentanyl may reduce midazolam clearance.

Antiepileptics: Co-administration with midazolam may cause enhanced sedation or respiratory or cardiovascular depression. Midazolam may interact with other hepatically metabolised medicinal products, e.g. phenytoin, causing potentiation.

Calcium-channel blockers: Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Dopaminergic agents: Midazolam may cause inhibition of levodopa.

Muscle relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabilone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing medicinal products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Medicinal products s that inhibit CYP3A4

Medicinal product interactions following oromucosal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Azole antifungals

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.

Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.

Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide antibiotics

Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.

Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

HIV Protease inhibitors

Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

Calcium-channel blockers

Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Various medicinal products

Atorvastatin showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

Medicinal products that induce CYP3A4

Rifampicin (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

Herb and food

St John’s Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half life of about 15-17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).
Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

The effect of CYP3A4 inhibitors may be larger in infants since part of the oromucosal dose is probably swallowed and absorbed in the gastro-intestinal tract.

4.6 Fertility, pregnancy and lactation

Pregnancy
Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the new-born infant).

Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Breastfeeding
Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Fertility
Animal studies did not show an impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

4.8 Undesirable effects

Published clinical studies show that oromucosal midazolam was administered to approx 443 children with seizures. Most studies did not indicate numbers of adverse reactions but stated that no severe events had been reported or there was no difference from the active comparator, rectal or intravenous diazepam. Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. One episode of pruritus was possibly attributed to the use of buccal midazolam.

The table below lists the adverse reactions reported to occur when oromucosal midazolam was administered to children in clinical studies.

The frequency of adverse reactions is classified as follows:
Common: $\geq 1/100$ to $< 1/10$
Uncommon: $\geq 1/1,000$ to $< 1/100$
Very rare: $\leq 1/10,000$

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness;

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6
Nervous system disorders
Common:
- Sedation, somnolence, depressed levels of consciousness
- Respiratory depression

Gastrointestinal disorders
Common:
- Nausea and vomiting

Skin and subcutaneous tissue disorders
Uncommon:
- Pruritus, rash and urticaria

The following adverse reactions have been reported to occur (very rarely) when midazolam is injected in children and or adults, which may be of relevance to oromucosal administration:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: Adverse Drug Reaction - All occur very rarely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>aggression, agitation, anger, confusional state, euphoric mood, hallucination, hostility, movement disorder, physical assault.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>anterograde amnesia, ataxia, dizziness, headache, seizure, paradoxical reactions.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>bradycardia, cardiac arrest, hypotension, vasodilatation</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>apnoea, dyspnoea, laryngospasm, respiratory arrest,</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>constipation, dry mouth</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>fatigue, hiccups</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dosage is administered (see section 4.4).

4.9 Overdose

Midazolam overdose should not present a threat to life unless the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. Flumazenil may be useful as an antidote.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: Not yet assigned.

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form the hydrochloride salt with acids. These produce a stable solution suitable for oromucosal administration.

The pharmacological action of midazolam is characterized by short duration because of rapid metabolic transformation. Midazolam has an anticonvulsant effect. It also exerts a sedative and sleep-inducing effect of pronounced intensity, and an anxiolytic and a muscle-relaxant effect.

In 4 rectal diazepam controlled studies and one study versus intravenous diazepam, in a total of 688 children, cessation of visible signs of seizures within 10 minutes was observed in 65% to 78% of children receiving oromucosal midazolam. Additionally, in 2 of the studies, cessation of visible signs of seizures within 10 minutes without recurrence within 1 hour after administration was observed in 56% to 70% of children. The frequency and severity of adverse drug reactions reported for Oromucosal midazolam during published clinical trials were similar to the adverse drug reactions reported in the comparative group using rectal diazepam.

The European Medicines Agency has waived the obligation to submit the results of studies with BUCCOLAM in the subset of the paediatric population < 3months old, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for these paediatric patients. The treatment of infants between 3-6 months of age should be provided only under the supervision of a health care professional in a hospital setting where resuscitation equipment is available. See section 4.2.

5.2 Pharmacokinetic properties

Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years, based on a population pharmacokinetic study are provided in tabulated format below:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>3 m &lt; 1 yr</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>168</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>104</td>
<td>46</td>
</tr>
<tr>
<td>5 mg</td>
<td>1 yr &lt; 5 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>242</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>148</td>
<td>62</td>
</tr>
<tr>
<td>7.5 mg</td>
<td>5 yrs &lt;10 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>254</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>140</td>
<td>60</td>
</tr>
<tr>
<td>10 mg</td>
<td>10 yrs &lt;18 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>189</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>87</td>
<td>44</td>
</tr>
</tbody>
</table>

Absorption after oromucosal administration

After oromucosal administration midazolam is absorbed rapidly. Maximum plasma concentration is reached within 30 minutes in children. The absolute bioavailability of oromucosal midazolam is about
75% in adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

**Distribution**
Midazolam is highly lipophilic and distributes extensively. The steady state volume of distribution following oromucosal administration is estimated to be 5.3 l/kg.

Approximately 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

**Metabolism**
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxy-midazolam. Following oromucosal administration in children the area under the curve ratio for alpha-hydroxy midazolam to midazolam is 0.46.

In a population pharmacokinetic study, the metabolite levels are shown to be higher in younger than older paediatric patients and thus likely to be of more importance in children than in adults.

**Elimination**
Plasma clearance of midazolam in children following oromucosal administration is 30 ml/kg/min. The initial and terminal elimination half-lives are 27 and 204 minutes, respectively. Midazolam is excreted mainly by the renal route (60-80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxy-midazolam. Less than 1% of the dose is recovered in urine as unchanged medicinal product.

**Pharmacokinetics in special populations**

**Obese**
The mean half-life is greater in obese than in non-obese patients (5.9 versus 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

**Patients with hepatic impairment**
The elimination half-life in cirrhotic patients may be longer and the clearance lower as compared to those in healthy volunteers (see section 4.4).

**Patients with renal impairment**
The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

**Patients with cardiac insufficiency**
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

**Exposure following a second dose in the same seizure episode**
Simulated exposure data show that the overall AUC approximately doubles when a second dose is administered at 10, 30 and 60 minutes following the first dose. A second dose at 10 minutes results in a significant increase in mean $C_{\text{max}}$ of between 1.7 to 1.9 fold. At 30 and 60 minutes, significant elimination of midazolam has already occurred and therefore the increase in mean $C_{\text{max}}$ is less pronounced; 1.3 to 1.6 and 1.2 to 1.5 fold respectively. (see section 4.2).
5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (for pH adjustment and conversion of midazolam to the hydrochloride salt)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage:

Keep the oral syringe in the protective plastic tube.
Do not refrigerate or freeze.

6.5 Nature and contents of container:

Amber, pre-filled needle-free oral syringe (polypropylene) with plunger (polypropylene) and end cap (high density polyethylene) packed in a protective, capped plastic tube.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of solution</th>
<th>Syringe volume</th>
<th>Age range</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>0.5 ml</td>
<td>1 ml</td>
<td>3 months to &lt; 1 year</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

BUCCOLAM is available in cartons containing 4 pre-filled syringes.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViroPharma SPRL
rue Montoyer 47
1000 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)
EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE TEXT

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. **NAME OF THE MEDICINAL PRODUCT**

BUCCOLAM 5 mg oromucosal solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each pre-filled oral syringe contains 5 mg midazolam (as hydrochloride) in 1 ml solution

For a full list of excipients, see section 6.1

3. **PHARMACEUTICAL FORM**

Oromucosal solution
Clear colourless solution
pH 2.9 to 3.7

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy

For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. See section 4.2

4.2 Posology and method of administration

**Posology**

Standard doses are indicated below:

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<td>10 years to &lt; 18 years</td>
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</tr>
</tbody>
</table>

Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought and the empty syringe given to the healthcare professional to provide information on the dose received by the patient.
A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice (see section 5.2).

**Special populations**

**Paediatric population**
The safety and efficacy of midazolam in children aged 0 to 3 months has not been established. No data are available.

**Renal impairment**
No dose adjustment is required, however, BUCCOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged. (see section 4.4)

**Hepatic impairment**
Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment (see section 4.4). BUCCOLAM is contraindicated in patients with severe hepatic impairment (see section 4.3).

**Method of administration**
BUCCOLAM is for oromucosal use. The full amount of solution should be inserted slowly into the space between the gum and the cheek. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

**Precautions to be taken before manipulating or administering the product**
No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe.
BUCCOLAM is not for intravenous use.
The oral syringe cap should be removed before use to avoid risk of choking.

**4.3 Contraindications**
Hypersensitivity to the active substance, benzodiazepines or to any of the excipients.
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic impairment

**4.4 Special warnings and precautions for use**
Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of BUCCOLAM in the 3-6 month age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.
Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

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Muscle relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabilone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing medicinal products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Medicinal products that inhibit CYP3A4

Medicinal product interactions following oromucosal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Azole antifungals

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.

Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.

Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide antibiotics

Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.

Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

HIV Protease inhibitors

Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

Calcium-channel blockers

Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Various medicinal products

Atorvastatin showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

Medicinal products that induce CYP3A4

Rifampicin (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

Herb and food

St John’s Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half life of about 15-17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).
Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

The effect of CYP3A4 inhibitors may be larger in infants since part of the oromucosal dose is probably swallowed and absorbed in the gastro-intestinal tract.

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the new-born infant).

Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Breastfeeding

Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Fertility

Animal studies did not show an impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

4.8 Undesirable effects

Published clinical studies show that oromucosal midazolam was administered to approx 443 children with seizures. Most studies did not indicate numbers of adverse reactions but stated that no severe events had been reported or there was no difference from the active comparator, rectal or intravenous diazepam. Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. One episode of pruritus was possibly attributed to the use of buccal midazolam.

The table below lists the adverse reactions reported to occur when oromucosal midazolam was administered to children in clinical studies.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>≥ 1/100 to &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>≥ 1/1,000 to &lt; 1/100</td>
</tr>
<tr>
<td>Very rare:</td>
<td>≤ 1/10,000</td>
</tr>
</tbody>
</table>

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness;
Nervous system disorders

Common:
- Sedation, somnolence, depressed levels of consciousness
- Respiratory depression

Gastrointestinal disorders

Common:
- Nausea and vomiting

Skin and subcutaneous tissue disorders

Uncommon:
- Pruritus, rash and urticaria

The following adverse reactions have been reported to occur (very rarely) when midazolam is injected in children and or adults, which may be of relevance to oromucosal administration:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: Adverse Drug Reaction - All occur very rarely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>aggression, agitation, anger, confusional state, euphoric mood, hallucination, hostility, movement disorder, physical assault.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>anterograde amnesia, ataxia, dizziness, headache, seizure, paradoxical reactions.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>bradycardia, cardiac arrest, hypotension, vasodilatation</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>apnoea, dyspnoea, laryngospasm, respiratory arrest,</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>constipation, dry mouth</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>fatigue, hiccups</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dosage is administered (see section 4.4).

4.9 Overdose

Midazolam overdose should not present a threat to life unless the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. Flumazenil may be useful as an antidote.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: Not yet assigned.

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form the hydrochloride salt with acids. These produce a stable solution suitable for oromucosal administration.

The pharmacological action of midazolam is characterized by short duration because of rapid metabolic transformation. Midazolam has an anticonvulsant effect. It also exerts a sedative and sleep-inducing effect of pronounced intensity, and an anxiolytic and a muscle-relaxant effect.

In 4 rectal diazepam controlled studies and one study versus intravenous diazepam, in a total of 688 children, cessation of visible signs of seizures within 10 minutes was observed in 65% to 78% of children receiving oromucosal midazolam. Additionally, in 2 of the studies, cessation of visible signs of seizures within 10 minutes without recurrence within 1 hour after administration was observed in 56% to 70% of children. The frequency and severity of adverse drug reactions reported for Oromucosal midazolam during published clinical trials were similar to the adverse drug reactions reported in the comparative group using rectal diazepam.

The European Medicines Agency has waived the obligation to submit the results of studies with BUCCOLAM in the subset of the paediatric population < 3months old, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for these paediatric patients. The treatment of infants between 3-6 months of age should be provided only under the supervision of a health care professional in a hospital setting where resuscitation equipment is available. See section 4.2.

5.2 Pharmacokinetic properties

Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years, based on a population pharmacokinetic study are provided in tabulated format below:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>3 m &lt; 1 yr</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>168</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>104</td>
<td>46</td>
</tr>
<tr>
<td>5 mg</td>
<td>1 yr &lt; 5 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>242</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>148</td>
<td>62</td>
</tr>
<tr>
<td>7.5 mg</td>
<td>5 yrs &lt;10 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>254</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>140</td>
<td>60</td>
</tr>
<tr>
<td>10 mg</td>
<td>10 yrs &lt;18 yrs</td>
<td>AUC_{0-inf} (ng.h/ml)</td>
<td>189</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C_{max} (ng/ml)</td>
<td>87</td>
<td>44</td>
</tr>
</tbody>
</table>

Absorption after oromucosal administration

After oromucosal administration midazolam is absorbed rapidly. Maximum plasma concentration is reached within 30 minutes in children. The absolute bioavailability of oromucosal midazolam is about
75% in adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

**Distribution**
Midazolam is highly lipophilic and distributes extensively. The steady state volume of distribution following oromucosal administration is estimated to be 5.3 l/kg.

Approximately 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

**Metabolism**
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxy-midazolam. Following oromucosal administration in children the area under the curve ratio for alpha-hydroxy midazolam to midazolam is 0.46.

In a population pharmacokinetic study, the metabolite levels are shown to be higher in younger than older paediatric patients and thus likely to be of more importance in children than in adults.

**Elimination**
Plasma clearance of midazolam in children following oromucosal administration is 30 ml/kg/min. The initial and terminal elimination half-lives are 27 and 204 minutes, respectively. Midazolam is excreted mainly by the renal route (60-80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxy-midazolam. Less than 1% of the dose is recovered in urine as unchanged medicinal product.

**Pharmacokinetics in special populations**

*Obese*
The mean half-life is greater in obese than in non-obese patients (5.9 versus 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

*Patients with hepatic impairment*
The elimination half-life in cirrhotic patients may be longer and the clearance lower as compared to those in healthy volunteers (see section 4.4).

*Patients with renal impairment*
The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

*Patients with cardiac insufficiency*
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

*Exposure following a second dose in the same seizure episode*
Simulated exposure data show that the overall AUC approximately doubles when a second dose is administered at 10, 30 and 60 minutes following the first dose. A second dose at 10 minutes results in a significant increase in mean C\text{max} of between 1.7 to 1.9 fold. At 30 and 60 minutes, significant elimination of midazolam has already occurred and therefore the increase in mean C\text{max} is less pronounced; 1.3 to 1.6 and 1.2 to 1.5 fold respectively. (see section 4.2).
5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride  
Water for injections  
Hydrochloric acid (for pH adjustment and conversion of midazolam to the hydrochloride salt)  
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage:

Keep the oral syringe in the protective plastic tube.  
Do not refrigerate or freeze.

6.5 Nature and contents of container:

Amber, pre-filled needle-free oral syringe (polypropylene) with plunger (polypropylene) and end cap (high density polyethylene) packed in a protective, capped plastic tube.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of solution</th>
<th>Syringe volume</th>
<th>Age range</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>1 ml</td>
<td>3 ml</td>
<td>1 year to &lt; 5 years</td>
<td>Blue</td>
</tr>
</tbody>
</table>

BUCCOLAM is available in cartons containing 4 pre-filled syringes.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViroPharma SPRL  
rue Montoyer 47  
1000 Brussels  
Belgium

8. MARKETING AUTHORISATION NUMBER(S)
EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE TEXT

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. **NAME OF THE MEDICINAL PRODUCT**

BUCCOLAM 7.5 mg oromucosal solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each pre-filled oral syringe contains 7.5 mg midazolam (as hydrochloride) in 1.5 ml solution

For a full list of excipients, see section 6.1

3. **PHARMACEUTICAL FORM**

Oromucosal solution
Clear colourless solution
pH 2.9 to 3.7

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy

For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. See section 4.2

4.2 **Posology and method of administration**

**Posology**

Standard doses are indicated below:

<table>
<thead>
<tr>
<th>Age range</th>
<th>Dose</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 6 months</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>hospital setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 months to &lt; 1 year</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>1 year to &lt; 5 years</td>
<td>5 mg</td>
<td>Blue</td>
</tr>
<tr>
<td>5 years to &lt; 10 years</td>
<td>7.5 mg</td>
<td>Purple</td>
</tr>
<tr>
<td>10 years to &lt; 18 years</td>
<td>10 mg</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought and the empty syringe given to the healthcare professional to provide information on the dose received by the patient.
A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice (see section 5.2).

**Special populations**

**Paediatric population**
The safety and efficacy of midazolam in children aged 0 to 3 months has not been established. No data are available.

**Renal impairment**
No dose adjustment is required, however, BUCCOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged. (see section 4.4)

**Hepatic impairment**
Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment (see section 4.4). BUCCOLAM is contraindicated in patients with severe hepatic impairment (see section 4.3).

**Method of administration**
BUCCOLAM is for oromucosal use. The full amount of solution should be inserted slowly into the space between the gum and the cheek. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

**Precautions to be taken before manipulating or administering the product**
No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe.
BUCCOLAM is not for intravenous use.
The oral syringe cap should be removed before use to avoid risk of choking.

### 4.3 Contraindications
Hypersensitivity to the active substance, benzodiazepines or to any of the excipients.
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic impairment

### 4.4 Special warnings and precautions for use
Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of BUCCOLAM in the 3-6 month age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.
Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

4.5 Interaction with other medicinal products and other forms of interaction

Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, a careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Anaesthetics and narcotic analgesics: Fentanyl may reduce midazolam clearance.

Antiepileptics: Co-administration with midazolam may cause enhanced sedation or respiratory or cardiovascular depression. Midazolam may interact with other hepatically metabolised medicinal products, e.g. phenytoin, causing potentiation.

Calcium-channel blockers: Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Dopaminergic agents: Midazolam may cause inhibition of levodopa.

Muscle relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabilone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing medicinal products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Medicinal products that inhibit CYP3A4

Medicinal product interactions following oromucosal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Azole antifungals

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.

Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
**Fluconazole and itraconazole** both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.

**Posaconazole** increased the plasma concentrations of intravenous midazolam by about 2-fold.

**Macrolide antibiotics**

**Erythromycin** resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.

**Clarithromycin** increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

**HIV Protease inhibitors**

Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

**Calcium-channel blockers**

**Diltiazem**: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

**Various medicinal products**

**Atorvastatin** showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

**Medicinal products that induce CYP3A4**

**Rifampicin** (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

**Herb and food**

St John’s Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half-life of about 15-17%. Depending on the specific St John’s Wort extract, the CYP3A4-inducing effect may vary.

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

**Pharmacodynamic Drug-Drug Interactions (DDI)**

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).
Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics. The effect of CYP3A4 inhibitors may be larger in infants since part of the oromucosal dose is probably swallowed and absorbed in the gastro-intestinal tract.

4.6 Fertility, pregnancy and lactation

Pregnancy
Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the new-born infant).

Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Breastfeeding
Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Fertility
Animal studies did not show an impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

4.8 Undesirable effects

Published clinical studies show that oromucosal midazolam was administered to approx 443 children with seizures. Most studies did not indicate numbers of adverse reactions but stated that no severe events had been reported or there was no difference from the active comparator, rectal or intravenous diazepam. Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. One episode of pruritus was possibly attributed to the use of buccal midazolam.

The table below lists the adverse reactions reported to occur when oromucosal midazolam was administered to children in clinical studies.

The frequency of adverse reactions is classified as follows:

- **Common:** $\geq 1/100$ to $< 1/10$
- **Uncommon:** $\geq 1/1,000$ to $< 1/100$
- **Very rare:** $\leq 1/10,000$

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nervous system disorders | Common:
Sedation, somnolence, depressed levels of consciousness
Respiratory depression

Gastrointestinal disorders | Common:
Nausea and vomiting

Skin and subcutaneous tissue disorders | Uncommon:
Pruritus, rash and urticaria

The following adverse reactions have been reported to occur (very rarely) when midazolam is injected in children and or adults, which may be of relevance to oromucosal administration:

<table>
<thead>
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<th>Frequency: Adverse Drug Reaction - All occur very rarely</th>
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<td>anterograde amnesia, ataxia, dizziness, headache, seizure, paradoxical reactions.</td>
</tr>
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</tr>
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<td>fatigue, hiccups</td>
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Description of selected adverse reactions

An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dosage is administered (see section 4.4).

4.9 Overdose

Midazolam overdose should not present a threat to life unless the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. Flumazenil may be useful as an antidote.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: Not yet assigned.

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form the hydrochloride salt with acids. These produce a stable solution suitable for oromucosal administration.

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In 4 rectal diazepam controlled studies and one study versus intravenous diazepam, in a total of 688 children, cessation of visible signs of seizures within 10 minutes was observed in 65% to 78% of children receiving oromucosal midazolam. Additionally, in 2 of the studies, cessation of visible signs of seizures within 10 minutes without recurrence within 1 hour after administration was observed in 56% to 70% of children. The frequency and severity of adverse drug reactions reported for oromucosal midazolam during published clinical trials were similar to the adverse drug reactions reported in the comparative group using rectal diazepam.

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5.2 Pharmacokinetic properties

Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years, based on a population pharmacokinetic study are provided in tabulated format below:

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Absorption after oromucosal administration

After oromucosal administration midazolam is absorbed rapidly. Maximum plasma concentration is reached within 30 minutes in children. The absolute bioavailability of oromucosal midazolam is about
75% in adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

**Distribution**
Midazolam is highly lipophilic and distributes extensively. The steady state volume of distribution following oromucosal administration is estimated to be 5.3 l/kg.

Approximately 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

**Metabolism**
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxy-midazolam. Following oromucosal administration in children the area under the curve ratio for alpha-hydroxy midazolam to midazolam is 0.46.

In a population pharmacokinetic study, the metabolite levels are shown to be higher in younger than older paediatric patients and thus likely to be of more importance in children than in adults.

**Elimination**
Plasma clearance of midazolam in children following oromucosal administration is 30 ml/kg/min. The initial and terminal elimination half-lives are 27 and 204 minutes, respectively. Midazolam is excreted mainly by the renal route (60-80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxy-midazolam. Less than 1% of the dose is recovered in urine as unchanged medicinal product.

**Pharmacokinetics in special populations**

**Obese**
The mean half-life is greater in obese than in non-obese patients (5.9 versus 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

**Patients with hepatic impairment**
The elimination half-life in cirrhotic patients may be longer and the clearance lower as compared to those in healthy volunteers (see section 4.4).

**Patients with renal impairment**
The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

**Patients with cardiac insufficiency**
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

**Exposed following a second dose in the same seizure episode**
Simulated exposure data show that the overall AUC approximately doubles when a second dose is administered at 10, 30 and 60 minutes following the first dose. A second dose at 10 minutes results in a significant increase in mean C_{max} of between 1.7 to 1.9 fold. At 30 and 60 minutes, significant elimination of midazolam has already occurred and therefore the increase in mean C_{max} is less pronounced; 1.3 to 1.6 and 1.2 to 1.5 fold respectively. (see section 4.2).
5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (for pH adjustment and conversion of midazolam to the hydrochloride salt)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage:

Keep the oral syringe in the protective plastic tube.
Do not refrigerate or freeze.

6.5 Nature and contents of container:

Amber, pre-filled needle-free oral syringe (polypropylene) with plunger (polypropylene) and end cap (high density polyethylene) packed in a protective, capped plastic tube.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of solution</th>
<th>Syringe volume</th>
<th>Age range</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 mg</td>
<td>1.5 ml</td>
<td>3 ml</td>
<td>5 years to &lt; 10 years</td>
<td>Purple</td>
</tr>
</tbody>
</table>

BUCCOLAM is available in cartons containing 4 pre-filled syringes.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViroPharma SPRL
rue Montoyer 47
1000 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)
EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE TEXT

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT
BUCCOLAM 10 mg oromucosal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each pre-filled oral syringe contains 10 mg midazolam (as hydrochloride) in 2 ml solution
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Oromucosal solution
Clear colourless solution
pH 2.9 to 3.7

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)
BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy
For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. See section 4.2

4.2 Posology and method of administration
Posology
Standard doses are indicated below:

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<tr>
<th>Age range</th>
<th>Dose</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 6 months</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>hospital setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 months to &lt; 1 year</td>
<td>2.5mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>1 year to &lt; 5 years</td>
<td>5 mg</td>
<td>Blue</td>
</tr>
<tr>
<td>5 years to &lt; 10 years</td>
<td>7.5 mg</td>
<td>Purple</td>
</tr>
<tr>
<td>10 years to &lt; 18 years</td>
<td>10 mg</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought and the empty syringe given to the healthcare professional to provide information on the dose received by the patient.
A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice (see section 5.2).

**Special populations**

**Paediatric population**
The safety and efficacy of midazolam in children aged 0 to 3 months has not been established. No data are available.

**Renal impairment**
No dose adjustment is required, however, BUCCOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged. (see section 4.4)

**Hepatic impairment**
Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment (see section 4.4). BUCCOLAM is contraindicated in patients with severe hepatic impairment (see section 4.3).

**Method of administration**
BUCCOLAM is for oromucosal use. The full amount of solution should be inserted slowly into the space between the gum and the cheek. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

**Precautions to be taken before manipulating or administering the product**
No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe.
BUCCOLAM is not for intravenous use.
The oral syringe cap should be removed before use to avoid risk of choking.

### 4.3 Contraindications

Hypersensitivity to the active substance, benzodiazepines or to any of the excipients.
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic impairment

### 4.4 Special warnings and precautions for use

Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of BUCCOLAM in the 3-6 month age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.
Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

4.5 Interaction with other medicinal products and other forms of interaction

Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, a careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Anaesthetics and narcotic analgesics: Fentanyl may reduce midazolam clearance.

Antiepileptics: Co-administration with midazolam may cause enhanced sedation or respiratory or cardiovascular depression. Midazolam may interact with other hepatically metabolised medicinal products, e.g. phenytoin, causing potentiation.

Calcium-channel blockers: Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Dopaminergic agents: Midazolam may cause inhibition of levodopa.

Muscle relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabilone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing medicinal products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Medicinal products s that inhibit CYP3A4

Medicinal product interactions following oromucosal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Aazole antifungals

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.

Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.

Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide antibiotics

Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.

Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

HIV Protease inhibitors

Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

Calcium-channel blockers

Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Various medicinal products

Atorvastatin showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

Medicinal products that induce CYP3A4

Rifampicin (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

Herb and food

St John’s Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half life of about 15-17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).
Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

The effect of CYP3A4 inhibitors may be larger in infants since part of the oromucosal dose is probably swallowed and absorbed in the gastro-intestinal tract.

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the new-born infant).

Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Breastfeeding

Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Fertility

Animal studies did not show an impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

4.8 Undesirable effects

Published clinical studies show that oromucosal midazolam was administered to approx 443 children with seizures. Most studies did not indicate numbers of adverse reactions but stated that no severe events had been reported or there was no difference from the active comparator, rectal or intravenous diazepam. Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. One episode of pruritus was possibly attributed to the use of buccal midazolam.

The table below lists the adverse reactions reported to occur when oromucosal midazolam was administered to children in clinical studies.

The frequency of adverse reactions is classified as follows:

| Common: | ≥ 1/100 to < 1/10 |
| Uncommon: | ≥ 1/1,000 to < 1/100 |
| Very rare: | ≤ 1/10,000 |

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness;
Nervous system disorders
Common:
Sedation, somnolence, depressed levels of consciousness
Respiratory depression

Gastrointestinal disorders
Common:
Nausea and vomiting

Skin and subcutaneous tissue disorders
Uncommon:
Pruritus, rash and urticaria

The following adverse reactions have been reported to occur (very rarely) when midazolam is injected in children and or adults, which may be of relevance to oromucosal administration:

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Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dosage is administered (see section 4.4).

4.9 Overdose

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In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

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75% in adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

**Distribution**
Midazolam is highly lipophilic and distributes extensively. The steady state volume of distribution following oromucosal administration is estimated to be 5.3 l/kg.

Approximately 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

**Metabolism**
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxy-midazolam. Following oromucosal administration in children the area under the curve ratio for alpha-hydroxy midazolam to midazolam is 0.46.

In a population pharmacokinetic study, the metabolite levels are shown to be higher in younger than older paediatric patients and thus likely to be of more importance in children than in adults.

**Elimination**
Plasma clearance of midazolam in children following oromucosal administration is 30 ml/kg/min. The initial and terminal elimination half-lives are 27 and 204 minutes, respectively. Midazolam is excreted mainly by the renal route (60-80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxy-midazolam. Less than 1% of the dose is recovered in urine as unchanged medicinal product.

**Pharmacokinetics in special populations**

**Obese**
The mean half-life is greater in obese than in non-obese patients (5.9 versus 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

**Patients with hepatic impairment**
The elimination half-life in cirrhotic patients may be longer and the clearance lower as compared to those in healthy volunteers (see section 4.4).

**Patients with renal impairment**
The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

**Patients with cardiac insufficiency**
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

**Exposure following a second dose in the same seizure episode**
Simulated exposure data show that the overall AUC approximately doubles when a second dose is administered at 10, 30 and 60 minutes following the first dose. A second dose at 10 minutes results in a significant increase in mean $C_{\text{max}}$ of between 1.7 to 1.9 fold. At 30 and 60 minutes, significant elimination of midazolam has already occurred and therefore the increase in mean $C_{\text{max}}$ is less pronounced; 1.3 to 1.6 and 1.2 to 1.5 fold respectively. (see section 4.2).
5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (for pH adjustment and conversion of midazolam to the hydrochloride salt)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage:

Keep the oral syringe in the protective plastic tube.
Do not refrigerate or freeze.

6.5 Nature and contents of container:

Amber, pre-filled needle-free oral syringe (polypropylene) with plunger (polypropylene) and end cap (high density polyethylene) packed in a protective, capped plastic tube.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of solution</th>
<th>Syringe volume</th>
<th>Age range</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>2 ml</td>
<td>3 ml</td>
<td>10 years to &lt; 18 years</td>
<td>Orange</td>
</tr>
</tbody>
</table>

BUCCOLAM is available in cartons containing 4 pre-filled syringes.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViroPharma SPRL
rue Montoyer 47
1000 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)
EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE TEXT

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
A. Manufacturer responsible for batch release

Name and address of the manufacturer responsible for batch release

Auralis Ltd.
Daresbury Innovation Centre
Keckwick Lane, Daresbury, Halton
Cheshire WA4 4FS
United Kingdom

B. Conditions or restrictions regarding supply and use

Strength 2.5 mg: Medicinal Product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Strengths 5mg, 7.5mg and 10 mg: Medicinal product subject to medical prescription.

C. Other conditions and requirements of the Marketing Authorisation

- **Pharmacovigilance system**
  The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

- **Risk Management Plan (RMP)**
  The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

  As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

  In addition, an updated RMP should be submitted
  - When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
  - Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
  - At the request of the European Medicines Agency.

- **PSURs**
  The PSUR cycle for the medicinal product should follow the standard requirements.

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**
  Not applicable.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (2.5 mg/0.5 ml)

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 2.5 mg oromucosal solution
Midazolam
For children aged 3 months to less than 1 year

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled, oral syringe (0.5 ml) contains 2.5 mg midazolam (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oromucosal solution
4 pre-filled oral syringes of 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oromucosal use only.
Each syringe is for single use only.
Remove the oral syringe cap before use to avoid risk of choking.

6. SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SITE OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.
| 10. | SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE. |
| 11. | NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER |
| | ViroPharma SPRL |
| | rue Montoyer 47 |
| | 1000 Brussels |
| | Belgium |
| 12. | MARKETING AUTHORIZATION NUMBER(S) |
| | EU/0/00/000/000 |
| 13. | BATCH NUMBER |
| | BN |
| 14. | GENERAL CLASSIFICATION FOR SUPPLY |
| | Medicinal product subject to medical prescription |
| 15. | INSTRUCTIONS ON USE |
| 16. | INFORMATION IN BRAILLE |
| | BUCCOLAM 2.5 mg |
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**Plastic Tube Label 2.5mg /0.5 ml**

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1. | **NAME OF THE MEDICINAL PRODUCT**
BUCCOLAM 2.5 mg oromucosal solution  
Midazolam  
For children aged 3 months to less than 1 year |
| 2. | **NAME OF THE MARKETING AUTHORISATION HOLDER**
ViroPharma logo |
| 3. | **EXPIRY DATE**
EXP |
| 4. | **BATCH NUMBER**
BN |
| 5. | **OTHER**
For oromucosal use only  
Remove the oral syringe cap before use  
Keep the oral syringe in the protective plastic tube |
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

Plastic oral syringe 2.5 mg/0.5 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 2.5 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 3 months to less than 1 year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use only</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use.</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</td>
</tr>
<tr>
<td>Carton (5 mg/1 ml)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

BUCCOLAM 5 mg oromucosal solution
Midazolam
For children aged 1 year to less than 5 years

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled, oral syringe (1 ml) contains 5 mg midazolam (as hydrochloride)

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

Oromucosal solution
4 pre-filled oral syringes of 1 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

For oromucosal use only
Each syringe is for single use only
Remove the oral syringe cap before use to avoid risk of choking

6. **SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SITE OF CHILDREN**

Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

ViroPharma SPRL
rue Montoyer 47
1000 Brussels
Belgium

12. MARKETING AUTHORIZATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 5 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plastic Tube Label 5mg /1 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 5 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 1 year to less than 5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViroPharma logo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use</td>
</tr>
<tr>
<td>Keep the oral syringe in the protective plastic tube</td>
</tr>
</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 5 mg/1 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 5 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 1 year to less than 5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use only.</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use.</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (7.5 mg/1.5 ml)

1. **NAME OF THE MEDICINAL PRODUCT**

BUCCOLAM 7.5 mg oromucosal solution
Midazolam
For children aged 5 years to less than 10 years

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled, oral syringe (1.5 ml) contains 7.5 mg midazolam (as hydrochloride)

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

Oromucosal solution
4 pre-filled oral syringes of 1.5 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

For oromucosal use only
Each syringe is for single use only
Remove the oral syringe cap before use to avoid risk of choking

6. **SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SITE OF CHILDREN**

Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   ViroPharma SPRL  
   rue Montoyer 47  
   1000 Brussels  
   Belgium

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/0/00/000/000

13. **BATCH NUMBER**

   BN

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   BUCCOLAM 7.5 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Plastic Tube Label 7.5mg /1.5 ml

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 7.5 mg oromucosal solution
Midazolam
For children aged 5 years to less than 10 years

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ViroPharma logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

For oromucosal use only
Remove the oral syringe cap before use
Keep the oral syringe in the protective plastic tube
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**Plastic oral syringe 7.5 mg/1.5 ml**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 7.5 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 5 years to less than 10 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use only</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use.</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (10 mg/2 ml)

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 10 mg oromucosal solution
Midazolam
For children aged 10 years to less than 18 years

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled, oral syringe (2 ml) contains 10 mg midazolam (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oromucosal solution
4 pre-filled oral syringes of 2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oromucosal use only
Each syringe is for single use only
Remove the oral syringe cap before use to avoid risk of choking

6. SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SITE OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.
<table>
<thead>
<tr>
<th>10.</th>
<th><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
</tbody>
</table>
|     | ViroPharma SPRL  
rue Montoyer 47  
1000 Brussels  
Belgium |
| 12. | **MARKETING AUTHORISATION NUMBER(S)** |
|     | EU/0/00/000/000 |
| 13. | **BATCH NUMBER** |
|     | BN |
| 14. | **GENERAL CLASSIFICATION FOR SUPPLY** |
|     | Medicinal product subject to medical prescription |
| 15. | **INSTRUCTIONS ON USE** |
| 16. | **INFORMATION IN BRAILLE** |
|     | BUCCOLAM 10 mg |
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**Plastic Tube Label 10mg /2 ml**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 10 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 10 year to less than 18 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViroPharma logo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use</td>
</tr>
<tr>
<td>Keep the oral syringe in the protective plastic tube</td>
</tr>
</tbody>
</table>
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 10 mg/2 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCOLAM 10 mg oromucosal solution</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>For children aged 10 years to less than 18 years</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oromucosal use only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use only.</td>
</tr>
<tr>
<td>Remove the oral syringe cap before use.</td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
1. WHAT BUCCOLAM IS AND WHAT IT IS USED FOR

What BUCCOLAM is
BUCCOLAM contains a medicine called midazolam. Midazolam belongs to a group of medicines known as benzodiazepines.

What is BUCCOLAM used for
BUCCOLAM is used to stop a prolonged, convulsive, seizure in infants, toddlers, children and adolescents (from 3 months to less than 18 years of age).

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

BUCCOLAM should only be used in infants from 3 months to less than 6 months in a hospital setting where monitoring is possible and resuscitation equipment is available.

2. BEFORE YOU GIVE BUCCOLAM

Do not give the patient BUCCOLAM
Do not give the patient BUCCOLAM and tell the doctor if the patient has:

- An allergy (hypersensitive) to midazolam, benzodiazepines (such as diazepam) or any of the other ingredients of BUCCOLAM (see section 6).
- A disease of the nerves and muscles causing muscle weakness (Myasthenia gravis).
- Difficulty breathing at rest (BUCCOLAM can make breathing difficulties worse).
- An illness causing frequent interruption of breathing during sleep (Sleep apnoea syndrome).
- Severe liver problems.

Take special care with BUCCOLAM

Before BUCCOLAM is given to the patient, check with their doctor or pharmacist if they have:
• A kidney, liver or heart condition.
• A lung condition that causes difficulty breathing on a regular basis.

BUCCOLAM may also cause people to forget what happened after they had been given this medicine. Patients should be observed carefully after being given BUCCOLAM.

Midazolam should not be given to patients with a medical history of alcohol or drug abuse.

If you are not sure if any of the above applies to the patient, talk to a doctor or pharmacist before giving BUCCOLAM.

Life threatening incidents are more likely in patients with breathing difficulties or heart problems, especially when higher doses of BUCCOLAM are given.

Children younger than 3 months: BUCCOLAM should not be given to children younger than 3 months since there is not enough information in this age group.

Taking other medicines
It is important to tell a doctor or pharmacist if the patient is taking, or has recently taken any other medicines. This includes medicines that can be bought without a prescription and herbal medicines. If you have any doubt about whether any medicine you or the patient is taking may affect the use of BUCCOLAM, please speak to your doctor or pharmacist.

This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved. For example, the effects of BUCCOLAM may be intensified by medicines such as:

- antiepileptics, (for treating epilepsy) e.g. phenytoin
- antibiotics, e.g. erythromycin, clarithromycin
- antifungals, e.g. ketoconazole, voriconazole, fluconazole, itraconazole, pozaconazole
- anti-ulcer medicines, e.g. cimetidine, ranitidine and omeprazole
- medicines used to treat blood pressure, e.g. diltiazem, verapamil
- some medicines used to treat HIV and AIDS, e.g. saquinavir, lopinavir/ritonavir combination
- narcotic analgesics (very strong pain killers), e.g. fentanyl
- medicines used to reduce fat in the blood, e.g. atorvastatin
- medicines used to treat nausea, e.g. nabilone

Some other medicines may also increase the effects of BUCCOLAM, e.g. hypnotics (sleep inducing medicines), sedative antidepressants (medicines to treat depression that make you sleepy), sedatives (medicines that relax you) anaesthetics and some antihistamines (medicines to treat of allergies)

Some medicines eg rifampicin (used to treat tuberculosis) and xanthines (used to treat asthma) may reduce the effect of BUCCOLAM.

St John’s Wort (a herbal medicine) may reduce the effect of BUCCOLAM and should be avoided in patients taking BUCCOLAM.

BUCCOLAM may also increase the effect of some muscle relaxants e.g. baclofen (causing increased drowsiness)

BUCCOLAM may stop some medicines from working as well, eg levodopa (a medicine used to treat Parkinsons disease)

Further information about these and about medicines the patient should avoid whilst taking BUCCOLAM can be obtained from a doctor or pharmacist.

Using BUCCOLAM with food and drink
Do not drink alcohol while you are taking BUCCOLAM. Alcohol may increase the sedative effects of BUCCOLAM and make you very sleepy.

Do not drink Grapefruit juice while taking BUCCOLAM. Grapefruit juice may increase the amount of BUCCOLAM in your blood and make you very sleepy.

**Pregnancy**

Tell a doctor if the patient who will be given this medicine is pregnant or could be pregnant. The doctor can decide if this medicine is suitable for her.

Giving high doses of BUCCOLAM during the last 3 months of pregnancy can cause abnormal heart beat in the unborn child. Babies born after BUCCOLAM is administered during childbirth can also have poor suckling, breathing difficulties and poor muscle tone at birth.

Ask your doctor or pharmacist for advice before taking any medicine.

**Breast-feeding**

Tell the doctor if the patient is breast-feeding. Even though small amounts of BUCCOLAM may pass into your breast milk, it may not be necessary to stop breast-feeding. The doctor will advise if the patient should breast-feed after being given BUCCOLAM.

**Driving and using machines**

BUCCOLAM may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving, riding a bicycle, or using machines. After receiving BUCCOLAM, the patient should not drive a vehicle, ride a bicycle or operate a machine until they have completely recovered. Please discuss with your doctor if you need further advice.

### 3. **HOW TO GIVE BUCCOLAM**

Always give BUCCOLAM exactly as a doctor has told you. You should check with a doctor or pharmacist if you are not sure.

The usual dose is:

**Patients:**

3 months to less than 1 year: 2.5 mg (yellow label)

Toddlers aged from 3 months to less than 6 months should only be treated in a hospital setting where monitoring is possible and resuscitation equipment is available. The usual dose in this situation: 2.5 mg (yellow label).

Your doctor will prescribe the most appropriate dose of BUCCOLAM. Do not give more than the amount of medicine prescribed by a doctor for the patient.

You should telephone for an ambulance immediately if any of the following occur:

- You cannot give BUCCOLAM.
- There is a possibility that you may have given too much BUCCOLAM.
- You cannot give all of the contents of the oral syringe.
- The child’s breathing slows down or stops.

**How to give this medicine**

Ask a doctor, pharmacist or nurse to show you how to take or administer this medicine. Always check with them if you are not sure.
Remove oral syringe cap before use to avoid risk of choking.

BUCCOLAM should be given in the side of the mouth (oromucosal use). Each oral syringe is pre-filled with the exact dose you need to give for ONE treatment. The full amount of medicine should be inserted slowly into the space between the gum and the cheek (see diagram). If necessary, about half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

Do not put a needle on the oral syringe. BUCCOLAM must not be injected.

If the seizure does not stop within 10 minutes of giving BUCCOLAM.
- You must telephone for an ambulance immediately.
- You must keep the empty oral syringe to give to the ambulance staff so that they know how much BUCCOLAM has been given.
- Do not give the patient another dose of BUCCOLAM.

If the patient is sick (vomits)
- Do not give the patient another dose of BUCCOLAM.

If you give too much
If you give too much BUCCOLAM
- You should telephone for an ambulance immediately.

Signs of overdose include:
- Absence of knee reflex or a response to a pinch.
- Breathing difficulties (slow or shallow breathing)
- Low blood pressure (giddiness and feeling faint)
- Coma.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

If you have any further questions on the use of this product, ask a doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines BUCCOLAM can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell a doctor or pharmacist.

A patient might have one or more of the following side effects after being given BUCCOLAM:

Common side effects (affects 1 to 10 users in 100):

- Severe breathing difficulties e.g. slow or shallow breathing or blue lips. In very rare cases breathing might stop. If breathing difficulties do occur seek medical assistance immediately (telephone for an ambulance).
- Feeling and being sick.
- The patient may be sleepy or less conscious.

Uncommon side effects (affects 1 to 10 users in 1,000):

Skin problems:
- rash
- hives (lumpy rash)
- itchiness

Very rare side effects (affects less than 1 user in 10,000):

Effects on behaviour:
- agitation
- restlessness
- hostility, rage or aggression
- excitement
- confusion
- euphoria (an excessive feeling of happiness or excitement)
- hallucinations (seeing and possibly hearing things that are not really there)

Muscle problems:
- muscle spasms and muscle tremors (shaking of your muscles that you cannot control).

Mental and nervous system problems:
- reduced alertness
- headache
- dizziness
- difficulty co-ordinating muscles
- fits (convulsions)
- temporary memory loss. How long this lasts depends on how much BUCCOLAM you were given. You may experience this after your treatment. In isolated cases this has been prolonged (lasted for a long time).

Heart and circulation problems:
Heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm.
- low blood pressure
- slow heart rate
- redness of the face and neck (flushing)

Breathing problems:
- shortness of breath
- In very rare cases breathing might stop.
• Laryngospasm (tightening of the vocal cords causing difficult and noisy breathing)

**Stomach, gut and mouth problems:**
• constipation
• dry mouth

**General:**
• tiredness.
• hiccups

5. **HOW TO STORE BUCCOLAM**

**Keep out of the reach and sight of children.**
Do not give BUCCOLAM after the expiry date which is stated on the carton, tube and oral syringe labels after EXP. The expiry date refers to the last day of that month.
Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.

BUCCOLAM should not be used if the packaging has been opened or damaged.

Disposal of oral syringes: medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What BUCCOLAM contains**
• The active substance is midazolam
• Each pre-filled oral syringe contains 2.5 mg midazolam (as hydrochloride) in 0.5 ml solution

The other ingredients are sodium chloride, water for injection, hydrochloric acid and sodium hydroxide (for pH adjustment).

**What BUCCOLAM looks like and contents of the pack**
BUCCOLAM oromucosal solution is a clear colourless liquid. It is supplied in an amber coloured pre-filled, single-use (needle-free) oral syringe. Each oral syringe is individually packed in a protective plastic tube. BUCCOLAM is available in cartons containing 4 pre-filled oral syringes/tubes (of the same dose).

**Marketing Authorisation Holder and Manufacturer**

ViroPharma SPRL
rue Montoyer 47
1000 Brussels
Belgium

Auralis Limited (a wholly owned subsidiary of ViroPharma Limited)
Daresbury Innovation Centre, Keckwick Lane,
Daresbury, Halton, Cheshire, WA4 4FS
UK

**This leaflet was last approved in**
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
1. WHAT BUCCOLAM IS AND WHAT IT IS USED FOR

What BUCCOLAM is
BUCCOLAM contains a medicine called midazolam. Midazolam belongs to a group of medicines known as benzodiazepines.

What is BUCCOLAM used for
BUCCOLAM is used to stop a prolonged, convulsive, seizure in infants, toddlers, children and adolescents (from 3 months to less than 18 years of age).

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

BUCCOLAM should only be used in infants from 3 months to less than 6 months in a hospital setting where monitoring is possible and resuscitation equipment is available.

2. BEFORE YOU GIVE BUCCOLAM

Do not give the patient BUCCOLAM
Do not give the patient BUCCOLAM and tell the doctor if the patient has:

- An allergy (hypersensitive) to midazolam, benzodiazepines (such as diazepam) or any of the other ingredients of BUCCOLAM (see section 6).
- A disease of the nerves and muscles causing muscle weakness (Myasthenia gravis).
- Difficulty breathing at rest (BUCCOLAM can make breathing difficulties worse).
- An illness causing frequent interruption of breathing during sleep (Sleep apnoea syndrome).
- Severe liver problems.

Take special care with BUCCOLAM

Before BUCCOLAM is given to the patient, check with their doctor or pharmacist if they have:
BUCCOLAM may also cause people to forget what happened after they had been given this medicine. Patients should be observed carefully after being given BUCCOLAM.

Midazolam should not be given to patients with a medical history of alcohol or drug abuse.

If you are not sure if any of the above applies to the patient, talk to a doctor or pharmacist before giving BUCCOLAM.

Life threatening incidents are more likely in patients with breathing difficulties or heart problems, especially when higher doses of BUCCOLAM are given.

Children younger than 3 months: BUCCOLAM should not be given to children younger than 3 months since there is not enough information in this age group.

Taking other medicines
It is important to tell a doctor or pharmacist if the patient is taking, or has recently taken any other medicines. This includes medicines that can be bought without a prescription and herbal medicines. If you have any doubt about whether any medicine you or the patient is taking may affect the use of BUCCOLAM, please speak to your doctor or pharmacist.

This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved. For example, the effects of BUCCOLAM may be intensified by medicines such as:

- antiepileptics, (for treating epilepsy) e.g. phenytoin
- antibiotics, e.g. erythromycin, clarithromycin
- antifungals, e.g. ketoconazole, voriconazole, fluconazole, itraconazole, pozaconazole
- anti-ulcer medicines, e.g. cimetidine, ranitidine and omeprazole
- medicines used to treat blood pressure, e.g. diltiazem, verapamil
- some medicines used to treat HIV and AIDS, e.g. saquinavir, lopinavir/ritonavir combination
- narcotic analgesics (very strong pain killers), e.g. fentanyl
- medicines used to reduce fat in the blood, e.g. atorvastatin
- medicines used to treat nausea, e.g. nabilone

Some other medicines may also increase the effects of BUCCOLAM, e.g. hypnotics (sleep inducing medicines), sedative antidepressants (medicines to treat depression that make you sleepy), sedatives (medicines that relax you) anaesthetics and some antihistamines (medicines to treat of allergies)

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BUCCOLAM may also increase the effect of some muscle relaxants e.g. baclofen (causing increased drowsiness)

BUCCOLAM may stop some medicines from working as well, eg levodopa (a medicine used to treat Parkinsons disease)

Further information about these and about medicines the patient should avoid whilst taking BUCCOLAM can be obtained from a doctor or pharmacist.

Using BUCCOLAM with food and drink
Do not drink alcohol while you are taking BUCCOLAM. Alcohol may increase the sedative effects of BUCCOLAM and make you very sleepy.

Do not drink Grapefruit juice while taking BUCCOLAM. Grapefruit juice may increase the amount of BUCCOLAM in your blood and make you very sleepy.

**Pregnancy**

Tell a doctor if the patient who will be given this medicine is pregnant or could be pregnant. The doctor can decide if this medicine is suitable for her.

Giving high doses of BUCCOLAM during the last 3 months of pregnancy can cause abnormal heart beat in the unborn child. Babies born after BUCCOLAM is administered during childbirth can also have poor suckling, breathing difficulties and poor muscle tone at birth.

Ask your doctor or pharmacist for advice before taking any medicine.

**Breast-feeding**

Tell the doctor if the patient is breast-feeding. Even though small amounts of BUCCOLAM may pass into your breast milk, it may not be necessary to stop breast-feeding. The doctor will advise if the patient should breast-feed after being given BUCCOLAM.

**Driving and using machines**

BUCCOLAM may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving, riding a bicycle, or using machines. After receiving BUCCOLAM, the patient should not drive a vehicle, ride a bicycle or operate a machine until they have completely recovered. Please discuss with your doctor if you need further advice.

### 3. HOW TO GIVE BUCCOLAM

Always give BUCCOLAM exactly as a doctor has told you. You should check with a doctor or pharmacist if you are not sure.

The usual dose is:

**Patients:**

- 1 year to less than 5 years: 5 mg (blue label)

Toddlers aged from 3 months to less than 6 months should only be treated in a hospital setting where monitoring is possible and resuscitation equipment is available. The usual dose in this situation:

- 2.5 mg (yellow label).

Your doctor will prescribe the most appropriate dose of BUCCOLAM.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

You should telephone for an ambulance immediately if any of the following occur:

- You cannot give BUCCOLAM.
- There is a possibility that you may have given too much BUCCOLAM.
- You cannot give all of the contents of the oral syringe.
- The child’s breathing slows down or stops.

**How to give this medicine**

Ask a doctor, pharmacist or nurse to show you how to take or administer this medicine. Always check with them if you are not sure.
Remove oral syringe cap before use to avoid risk of choking.

BUCCOLAM should be given in the side of the mouth (oromucosal use). Each oral syringe is pre-filled with the exact dose you need to give for ONE treatment. The full amount of medicine should be inserted slowly into the space between the gum and the cheek (see diagram). If necessary, about half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

Do not put a needle on the oral syringe. BUCCOLAM must not be injected.

If the seizure does not stop within 10 minutes of giving BUCCOLAM.
- You must telephone for an ambulance immediately.
- You must keep the empty oral syringe to give to the ambulance staff so that they know how much BUCCOLAM has been given.
- Do not give the patient another dose of BUCCOLAM.

If the patient is sick (vomits)
- Do not give the patient another dose of BUCCOLAM.

If you give too much
If you give too much BUCCOLAM
- You should telephone for an ambulance immediately.

Signs of overdose include:
- Absence of knee reflex or a response to a pinch.
- Breathing difficulties (slow or shallow breathing)
- Low blood pressure (giddiness and feeling faint)
- Coma.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

If you have any further questions on the use of this product, ask a doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines BUCCOLAM can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell a doctor or pharmacist.

A patient might have one or more of the following side effects after being given BUCCOLAM:

Common side effects (affects 1 to 10 users in 100):

- Severe breathing difficulties e.g. slow or shallow breathing or blue lips. In very rare cases breathing might stop. If breathing difficulties do occur seek medical assistance immediately (telephone for an ambulance).
- Feeling and being sick.
- The patient may be sleepy or less conscious.

Uncommon side effects (affects 1 to 10 users in 1,000):

**Skin problems:**
- rash
- hives (lumpy rash)
- itchiness

Very rare side effects (affects less than 1 user in 10,000):

**Effects on behaviour:**
- agitation
- restlessness
- hostility, rage or aggression
- excitement
- confusion
- euphoria (an excessive feeling of happiness or excitement)
- hallucinations (seeing and possibly hearing things that are not really there)

**Muscle problems:**
- muscle spasms and muscle tremors (shaking of your muscles that you cannot control).

**Mental and nervous system problems:**
- reduced alertness
- headache
- dizziness
- difficulty co-ordinating muscles
- fits (convulsions)
- temporary memory loss. How long this lasts depends on how much BUCCOLAM you were given. You may experience this after your treatment. In isolated cases this has been prolonged (lasted for a long time).

**Heart and circulation problems:**
Heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm.
- low blood pressure
- slow heart rate
- redness of the face and neck (flushing)

**Breathing problems:**
- shortness of breath
- In very rare cases breathing might stop.
• Laryngospasm (tightening of the vocal cords causing difficult and noisy breathing)

**Stomach, gut and mouth problems:**
• constipation
• dry mouth

**General:**
• tiredness.
• hiccups

5. **HOW TO STORE BUCCOLAM**

**Keep out of the reach and sight of children.**
Do not give BUCCOLAM after the expiry date which is stated on the carton, tube and oral syringe labels after EXP. The expiry date refers to the last day of that month. Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.

BUCCOLAM should not be used if the packaging has been opened or damaged.

Disposal of oral syringes: medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What BUCCOLAM contains**
• The active substance is midazolam
• Each pre-filled oral syringe contains 5 mg midazolam (as hydrochloride) in 1 ml solution.

The other ingredients are sodium chloride, water for injection, hydrochloric acid and sodium hydroxide (for pH adjustment).

**What BUCCOLAM looks like and contents of the pack**
BUCCOLAM oromucosal solution is a clear colourless liquid. It is supplied in an amber coloured pre-filled, single-use (needle-free) oral syringe. Each oral syringe is individually packed in a protective plastic tube. BUCCOLAM is available in cartons containing 4 pre-filled oral syringes/tubes (of the same dose).

**Marketing Authorisation Holder and Manufacturer**

ViroPharma SPRL
rue Montoyer 47
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Auralis Limited (a wholly owned subsidiary of ViroPharma Limited)
Daresbury Innovation Centre, Keckwick Lane,
Daresbury, Halton, Cheshire, WA4 4FS
UK

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1. **WHAT BUCCOLAM IS AND WHAT IT IS USED FOR**

What BUCCOLAM is
BUCCOLAM contains a medicine called midazolam. Midazolam belongs to a group of medicines known as benzodiazepines.

What is BUCCOLAM used for
BUCCOLAM is used to stop a prolonged, convulsive, seizure in infants, toddlers, children and adolescents (from 3 months to less than 18 years of age).

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

BUCCOLAM should only be used in infants from 3 months to less than 6 months in a hospital setting where monitoring is possible and resuscitation equipment is available.

2. **BEFORE YOU GIVE BUCCOLAM**

Do not give the patient BUCCOLAM
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Take special care with BUCCOLAM

Before BUCCOLAM is given to the patient, check with their doctor or pharmacist if they have:
BUCCOLAM may also cause people to forget what happened after they had been given this medicine. Patients should be observed carefully after being given BUCCOLAM.

Midazolam should not be given to patients with a medical history of alcohol or drug abuse.

If you are not sure if any of the above applies to the patient, talk to a doctor or pharmacist before giving BUCCOLAM.

Life threatening incidents are more likely in patients with breathing difficulties or heart problems, especially when higher doses of BUCCOLAM are given.

Children younger than 3 months: BUCCOLAM should not be given to children younger than 3 months since there is not enough information in this age group.

Taking other medicines
It is important to tell a doctor or pharmacist if the patient is taking, or has recently taken any other medicines. This includes medicines that can be bought without a prescription and herbal medicines. If you have any doubt about whether any medicine you or the patient is taking may affect the use of BUCCOLAM, please speak to your doctor or pharmacist.

This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved. For example, the effects of BUCCOLAM may be intensified by medicines such as:

- antiepileptics, (for treating epilepsy) e.g. phenytoin
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- some medicines used to treat HIV and AIDS, e.g. saquinavir, lopinavir/ritonavir combination
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- medicines used to treat nausea, e.g. nabilone

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Some medicines eg rifampicin (used to treat tuberculosis) and xanthines (used to treat asthma) may reduce the effect of BUCCOLAM.

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Using BUCCOLAM with food and drink
Do not drink alcohol while you are taking BUCCOLAM. Alcohol may increase the sedative effects of BUCCOLAM and make you very sleepy.

Do not drink Grapefruit juice while taking BUCCOLAM. Grapefruit juice may increase the amount of BUCCOLAM in your blood and make you very sleepy.

**Pregnancy**

Tell a doctor if the patient who will be given this medicine is pregnant or could be pregnant. The doctor can decide if this medicine is suitable for her.

Giving high doses of BUCCOLAM during the last 3 months of pregnancy can cause abnormal heart beat in the unborn child. Babies born after BUCCOLAM is administered during childbirth can also have poor suckling, breathing difficulties and poor muscle tone at birth.

Ask your doctor or pharmacist for advice before taking any medicine.

**Breast-feeding**

Tell the doctor if the patient is breast-feeding. Even though small amounts of BUCCOLAM may pass into your breast milk, it may not be necessary to stop breast-feeding. The doctor will advise if the patient should breast-feed after being given BUCCOLAM.

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BUCCOLAM may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving, riding a bicycle, or using machines. After receiving BUCCOLAM, the patient should not drive a vehicle, ride a bicycle or operate a machine until they have completely recovered. Please discuss with your doctor if you need further advice.

3. **HOW TO GIVE BUCCOLAM**

Always give BUCCOLAM exactly as a doctor has told you. You should check with a doctor or pharmacist if you are not sure.

The usual dose is:

**Patients:**
- 5 years to less than 10 years: 7.5 mg (purple label)

Toddlers aged from 3 months to less than 6 months should only be treated in a hospital setting where monitoring is possible and resuscitation equipment is available. The usual dose in this situation: 2.5 mg (yellow label).

Your doctor will prescribe the most appropriate dose of BUCCOLAM.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

You should telephone for an ambulance immediately if any of the following occur:
- You cannot give BUCCOLAM.
- There is a possibility that you may have given too much BUCCOLAM.
- You cannot give all of the contents of the oral syringe.
- The child’s breathing slows down or stops.

**How to give this medicine**

Ask a doctor, pharmacist or nurse to show you how to take or administer this medicine. Always check with them if you are not sure.
Remove oral syringe cap before use to avoid risk of choking.

BUCCOLAM should be given in the side of the mouth (oromucosal use). Each oral syringe is pre-filled with the exact dose you need to give for ONE treatment. The full amount of medicine should be inserted slowly into the space between the gum and the cheek (see diagram). If necessary, about half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

Do not put a needle on the oral syringe. BUCCOLAM must not be injected.

If the seizure does not stop within 10 minutes of giving BUCCOLAM.
- You must telephone for an ambulance immediately.
- You must keep the empty oral syringe to give to the ambulance staff so that they know how much BUCCOLAM has been given.
- Do not give the patient another dose of BUCCOLAM.

If the patient is sick (vomits)
- Do not give the patient another dose of BUCCOLAM.

If you give too much
If you give too much BUCCOLAM
- You should telephone for an ambulance immediately.

Signs of overdose include:
- Absence of knee reflex or a response to a pinch.
- Breathing difficulties (slow or shallow breathing)
- Low blood pressure (giddiness and feeling faint)
- Coma.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

If you have any further questions on the use of this product, ask a doctor or pharmacist.

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Like all medicines BUCCOLAM can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell a doctor or pharmacist.

A patient might have one or more of the following side effects after being given BUCCOLAM:

Common side effects (affects 1 to 10 users in 100):

- Severe breathing difficulties e.g. slow or shallow breathing or blue lips. In very rare cases breathing might stop. If breathing difficulties do occur seek medical assistance immediately (telephone for an ambulance).
- Feeling and being sick.
- The patient may be sleepy or less conscious.

Uncommon side effects (affects 1 to 10 users in 1,000):

**Skin problems:**
- rash
- hives (lumpy rash)
- itchiness

Very rare side effects (affects less than 1 user in 10,000):

**Effects on behaviour:**
- agitation
- restlessness
- hostility, rage or aggression
- excitement
- confusion
- euphoria (an excessive feeling of happiness or excitement)
- hallucinations (seeing and possibly hearing things that are not really there)

**Muscle problems:**
- muscle spasms and muscle tremors (shaking of your muscles that you cannot control).

**Mental and nervous system problems:**
- reduced alertness
- headache
- dizziness
- difficulty co-ordinating muscles
- fits (convulsions)
- temporary memory loss. How long this lasts depends on how much BUCCOLAM you were given. You may experience this after your treatment. In isolated cases this has been prolonged (lasted for a long time).

**Heart and circulation problems:**
Heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm.
- low blood pressure
- slow heart rate
- redness of the face and neck (flushing)

**Breathing problems:**
- shortness of breath
- In very rare cases breathing might stop.
• Laryngospasm (tightening of the vocal cords causing difficult and noisy breathing)

**Stomach, gut and mouth problems:**
• constipation
• dry mouth

**General:**
• tiredness.
• hiccups

5. **HOW TO STORE BUCCOLAM**

**Keep out of the reach and sight of children.**
Do not give BUCCOLAM after the expiry date which is stated on the carton, tube and oral syringe labels after EXP. The expiry date refers to the last day of that month.
Do not refrigerate or freeze.
Keep the oral syringe in the protective plastic tube.

BUCCOLAM should not be used if the packaging has been opened or damaged.

Disposal of oral syringes: medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What BUCCOLAM contains**
• The active substance is midazolam
• Each pre-filled oral syringe contains 7.5 mg midazolam (as hydrochloride) in 1.5 ml solution.

The other ingredients are sodium chloride, water for injection, hydrochloric acid and sodium hydroxide (for pH adjustment).

**What BUCCOLAM looks like and contents of the pack**
BUCCOLAM oromucosal solution is a clear colourless liquid. It is supplied in an amber coloured pre-filled, single-use (needle-free) oral syringe. Each oral syringe is individually packed in a protective plastic tube. BUCCOLAM is available in cartons containing 4 pre-filled oral syringes/tubes (of the same dose).

**Marketing Authorisation Holder and Manufacturer**

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**This leaflet was last approved in**
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
1. WHAT BUCCOLAM IS AND WHAT IT IS USED FOR

What BUCCOLAM is
BUCCOLAM contains a medicine called midazolam. Midazolam belongs to a group of medicines known as benzodiazepines.

What is BUCCOLAM used for
BUCCOLAM is used to stop a prolonged, convulsive, seizure in infants, toddlers, children and adolescents (from 3 months to less than 18 years of age).

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

BUCCOLAM should only be used in infants from 3 months to less than 6 months in a hospital setting where monitoring is possible and resuscitation equipment is available.

2. BEFORE YOU GIVE BUCCOLAM

Do not give the patient BUCCOLAM
Do not give the patient BUCCOLAM and tell the doctor if the patient has:

- An allergy (hypersensitive) to midazolam, benzodiazepines (such as diazepam) or any of the other ingredients of BUCCOLAM (see section 6).
- A disease of the nerves and muscles causing muscle weakness (Myasthenia gravis).
- Difficulty breathing at rest (BUCCOLAM can make breathing difficulties worse).
- An illness causing frequent interruption of breathing during sleep (Sleep apnoea syndrome).
- Severe liver problems.

Take special care with BUCCOLAM

Before BUCCOLAM is given to the patient, check with their doctor or pharmacist if they have:
• A kidney, liver or heart condition.
• A lung condition that causes difficulty breathing on a regular basis.

BUCCOLAM may also cause people to forget what happened after they had been given this medicine. Patients should be observed carefully after being given BUCCOLAM.

Midazolam should not be given to patients with a medical history of alcohol or drug abuse.

If you are not sure if any of the above applies to the patient, talk to a doctor or pharmacist before giving BUCCOLAM.

Life threatening incidents are more likely in patients with breathing difficulties or heart problems, especially when higher doses of BUCCOLAM are given.

Children younger than 3 months: BUCCOLAM should not be given to children younger than 3 months since there is not enough information in this age group.

Taking other medicines
It is important to tell a doctor or pharmacist if the patient is taking, or has recently taken any other medicines. This includes medicines that can be bought without a prescription and herbal medicines. If you have any doubt about whether any medicine you or the patient is taking may affect the use of BUCCOLAM, please speak to your doctor or pharmacist.

This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved. For example, the effects of BUCCOLAM may be intensified by medicines such as:

antiepileptics, (for treating epilepsy) e.g. phenytoin
antibiotics, e.g. erythromycin, clarithromycin
antifungals, e.g. ketoconazole, voriconazole, fluconazole, itraconazole, pozaconazole
anti-ulcer medicines, e.g. cimetidine, ranitidine and omeprazole
medicines used to treat blood pressure, e.g. diltiazem, verapamil
some medicines used to treat HIV and AIDS, e.g. saquinavir, lopinavir/ritonavir combination
narcotic analgesics (very strong pain killers), e.g. fentanyl
medicines used to reduce fat in the blood, e.g. atorvastatin
medicines used to treat nausea, e.g. nabilone

Some other medicines may also increase the effects of BUCCOLAM, e.g. hypnotics (sleep inducing medicines), sedative antidepressants (medicines to treat depression that make you sleepy), sedatives (medicines that relax you) anaesthetics and some antihistamines (medicines to treat of allergies)

Some medicines eg rifampicin (used to treat tuberculosis) and xanthines (used to treat asthma) may reduce the effect of BUCCOLAM.

St John’s Wort (a herbal medicine) may reduce the effect of BUCCOLAM and should be avoided in patients taking BUCCOLAM.

BUCCOLAM may also increase the effect of some muscle relaxants e.g. baclofen (causing increased drowsiness)

BUCCOLAM may stop some medicines from working as well, eg levodopa (a medicine used to treat Parkinsons disease)

Further information about these and about medicines the patient should avoid whilst taking BUCCOLAM can be obtained from a doctor or pharmacist.

Using BUCCOLAM with food and drink
Do not drink alcohol while you are taking BUCCOLAM. Alcohol may increase the sedative effects of BUCCOLAM and make you very sleepy.

Do not drink Grapefruit juice while taking BUCCOLAM. Grapefruit juice may increase the amount of BUCCOLAM in your blood and make you very sleepy.

**Pregnancy**

Tell a doctor if the patient who will be given this medicine is pregnant or could be pregnant. The doctor can decide if this medicine is suitable for her.

Giving high doses of BUCCOLAM during the last 3 months of pregnancy can cause abnormal heart beat in the unborn child. Babies born after BUCCOLAM is administered during childbirth can also have poor suckling, breathing difficulties and poor muscle tone at birth.

Ask your doctor or pharmacist for advice before taking any medicine.

**Breast-feeding**

Tell the doctor if the patient is breast-feeding. Even though small amounts of BUCCOLAM may pass into your breast milk, it may not be necessary to stop breast-feeding. The doctor will advise if the patient should breast-feed after being given BUCCOLAM.

**Driving and using machines**

BUCCOLAM may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving, riding a bicycle, or using machines. After receiving BUCCOLAM, the patient should not drive a vehicle, ride a bicycle or operate a machine until they have completely recovered. Please discuss with your doctor if you need further advice.

### 3. **HOW TO GIVE BUCCOLAM**

Always give BUCCOLAM exactly as a doctor has told you. You should check with a doctor or pharmacist if you are not sure.

The usual dose is:

**Patients:**

- 10 years to less than 18 years: 10 mg (orange label)
- Toddlers aged from 3 months to less than 6 months should only be treated in a hospital setting where monitoring is possible and resuscitation equipment is available. The usual dose in this situation: 2.5 mg (yellow label).

Your doctor will prescribe the most appropriate dose of BUCCOLAM.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

You should telephone for an ambulance immediately if any of the following occur:

- You cannot give BUCCOLAM.
- There is a possibility that you may have given too much BUCCOLAM.
- You cannot give all of the contents of the oral syringe.
- The child’s breathing slows down or stops.

**How to give this medicine**

Ask a doctor, pharmacist or nurse to show you how to take or administer this medicine. Always check with them if you are not sure.
Remove oral syringe cap before use to avoid risk of choking.

BUCCOLAM should be given in the side of the mouth (oromucosal use). Each oral syringe is pre-filled with the exact dose you need to give for ONE treatment. The full amount of medicine should be inserted slowly into the space between the gum and the cheek (see diagram). If necessary, about half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side.

Do not put a needle on the oral syringe. BUCCOLAM must not be injected.

If the seizure does not stop within 10 minutes of giving BUCCOLAM.
• You must telephone for an ambulance immediately.
• You must keep the empty oral syringe to give to the ambulance staff so that they know how much BUCCOLAM has been given.
• Do not give the patient another dose of BUCCOLAM.

If the patient is sick (vomits)
• Do not give the patient another dose of BUCCOLAM.

If you give too much
If you give too much BUCCOLAM
• You should telephone for an ambulance immediately.

Signs of overdose include:
• Absence of knee reflex or a response to a pinch.
• Breathing difficulties (slow or shallow breathing)
• Low blood pressure (giddiness and feeling faint)
• Coma.

Do not give more than the amount of medicine prescribed by a doctor for the patient.

If you have any further questions on the use of this product, ask a doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines BUCCOLAM can cause side effects, although not everybody gets them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell a doctor or pharmacist.

A patient might have one or more of the following side effects after being given BUCCOLAM:

Common side effects (affects 1 to 10 users in 100):

- Severe breathing difficulties e.g. slow or shallow breathing or blue lips. In very rare cases breathing might stop. If breathing difficulties do occur seek medical assistance immediately (telephone for an ambulance).
- Feeling and being sick.
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Uncommon side effects (affects 1 to 10 users in 1,000):

**Skin problems:**
- rash
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**Effects on behaviour:**
- agitation
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- reduced alertness
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**Heart and circulation problems:**
Heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm.
- low blood pressure
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- redness of the face and neck (flushing)

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- shortness of breath
- In very rare cases breathing might stop.
• Laryngospasm (tightening of the vocal cords causing difficult and noisy breathing)

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General:
• tiredness.
• hiccups

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Disposal of oral syringes: medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What BUCCOLAM contains
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• Each pre-filled oral syringe contains 10 mg midazolam (as hydrochloride) in 2 ml solution.

The other ingredients are sodium chloride, water for injection, hydrochloric acid and sodium hydroxide (for pH adjustment).

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