

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 2.5 mg oromucosal solution
BUCCOLAM 5 mg oromucosal solution
BUCCOLAM 7.5 mg oromucosal solution
BUCCOLAM 10 mg oromucosal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BUCCOLAM 2.5 mg oromucosal solution

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

BUCCOLAM 5 mg oromucosal solution

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

BUCCOLAM 7.5 mg oromucosal solution

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

BUCCOLAM 10 mg oromucosal solution

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oromucosal solution
Clear, colourless to yellowish solution
pH 2.9 to 3.7

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of prolonged, acute, convulsive seizures in infants from 3 months to adults.

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:

| Age range | Dose | Label colour |
|--------------------------------|-------------|---------------------|
| 3 to 6 months hospital setting | 2.5 mg | Yellow |
| > 6 months to < 1 year | 2.5 mg | Yellow |
| 1 year to < 5 years | 5 mg | Blue |
| 5 years to < 10 years | 7.5 mg | Purple |
| 10 years to adults | 10 mg | Orange |

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).

For patients at increased risk of respiratory depression from benzodiazepines, administration of BUCCOLAM under healthcare professional supervision should be considered prior to starting treatment with BUCCOLAM. This administration may be performed in the absence of a seizure.

Special populations

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).

Paediatric population

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

Elderly

The elderly are more sensitive to the effects of benzodiazepines. In patients from 60 years and in elderly patients BUCCOLAM should be used with caution.

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.

For detailed instructions on how to administer the medicinal product, see section 6.6.

Precautions to be taken before handling or administering the medicinal 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 listed in section 6.1
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic impairment

4.4 Special warnings and precautions for use

Special caution should be exercised when administering midazolam to high-risk patients:

- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
- paediatric patients with cardiovascular instability.

These high-risk patients may require lower dosages.

Respiratory insufficiency

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

Paediatric patients aged 3 to 6 months

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.

Altered elimination of midazolam

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.

Concomitant use with other benzodiazepines

Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

Medical history of alcohol or drug abuse

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

Amnesia

Midazolam may cause anterograde amnesia.

Excipients

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per oral syringe, that is to say essentially 'sodium-free'.

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.

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.

Dopaminergic medicinal products

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.

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.

Food

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

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

Co-administration with protease inhibitors (e.g. Saquinavir and other HIV 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

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%.

Herbs

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.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic medicinal products 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

There are no or limited amount of data from the use of midazolam in pregnant women. Animal studies do not indicate a teratogenic effect with respect to reproductive toxicity, but foetotoxicity has been observed in humans 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 suckling, 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.

Breast-feeding

Midazolam is excreted in low quantities (0.6%) in human 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

Summary of the safety profile

Published clinical studies show that oromucosal midazolam was administered to approximately 443 children and 224 adults with seizures. 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 midazolam use. One episode of pruritus was possibly attributed to the use of buccal midazolam.

Tabulated list of adverse reactions

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

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: $< 1/10,000$

Not known: cannot be estimated from the available data

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

| System Organ Class | Frequency: Adverse Drug Reaction |
|---|--|
| Psychiatric disorders | Very rare: Aggression**, agitation**, anger**, confusional state**, euphoric mood**, hallucination**, hostility**, movement disorder**, physical assault** |
| Nervous system disorders | Common: Sedation, somnolence, depressed levels of consciousness Respiratory depression Very rare: Anterograde amnesia**, ataxia**, dizziness**, headache**, seizure**, paradoxical reactions** |
| Cardiac disorders | Very rare: Bradycardia**, cardiac arrest**, hypotension**, vasodilatation** |
| Respiratory, thoracic and mediastinal disorders | Very rare: Apnoea**, dyspnea**, laryngospasm**, respiratory arrest** |
| Gastrointestinal disorders | Common: Nausea and vomiting Very rare: Constipation**, dry mouth** |
| Skin and subcutaneous tissue disorders | Uncommon: Pruritus, rash and urticarial Not known: Angioedema* |

| | |
|--|--------------------------------------|
| General disorders and administration site conditions | Very rare: Fatigue**, hiccups** |
| Immune system disorders | Not known: Anaphylactic reaction* |

***These adverse reactions have been reported to occur when midazolam is injected in children and/or adults, which may be of relevance to oromucosal administration.*

**ADR identified from postmarketing experience*

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

Midazolam overdose can present a threat to life if the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

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.

Management

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.

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, benzodiazepine derivatives ATC code: N05CD08.

Mechanism of action

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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

In four 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 two of the studies, cessation of visible signs of seizures within 10 minutes without recurrence within one 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 < 3 months old, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for these paediatric patients.

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, as well as pharmacokinetic parameters for the recommended posology in adults, based on a bioavailability study in healthy adult subjects, are provided in tabulated format below.

| Dose | Age | Parameter | Mean | SD |
|---------------|-----------------|--|-------------|-----------|
| 2.5 mg | 3 m < 1 yr | AUC _{0-inf} (ng.h/ml) | 168 | 98 |
| | | C _{max} (ng/ml) | 104 | 46 |
| 5 mg | 1 yr < 5 yrs | AUC _{0-inf} (ng.h/ml) | 242 | 116 |
| | | C _{max} (ng/ml) | 148 | 62 |
| 7.5 mg | 5 yrs <10 yrs | AUC _{0-inf} (ng.h/ml) | 254 | 136 |
| | | C _{max} (ng/ml) | 140 | 60 |
| 10 mg | 10 yrs < 18 yrs | AUC _{0-inf} (ng.h/ml) | 189 | 96 |
| | | C _{max} (ng/ml) | 87 | 44 |
| 10 mg | > 18 yrs | AUC _{0-inf} (ng.h/ml) (n=22) | 259 | 62 |
| | | C _{max} (ng/ml) (n=22) | 71 | 29 |

Simulated pharmacokinetic parameters for the recommended posology in adults (not elderly, not obese), based on a pharmacokinetic study, suggested that the dose of 10 mg in all adults lead to similar exposure to that of all pediatrics age groups at their corresponding therapeutic doses.

Absorption

After oromucosal administration midazolam is absorbed rapidly. Maximum plasma concentration is reached within 30 minutes. 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.

Biotransformation

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 the area under the curve ratio for alpha-hydroxy midazolam to midazolam is 0.46 in children and 0.28 in adults.

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

Elderly

Exposure to midazolam after oromucosal administration to adults between 60 and 70 years of age is similar to young adults. Exposure in older adults after oromucosal administration is unknown but may increase because after intravenous administration the elimination half-life may be prolonged up to four times.

Obese

The mean half life of midazolam after oromucosal administration to adults with a BMI between 30 and 34 is similar to adults with a BMI between 25 and 30 (8.4 versus 5.5 hours). The half life in adults with BMI above 34 is unknown but may increase because after intravenous administration 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.

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).

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.

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_{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).

Race

Clinical studies have included patients from Japanese and non-Japanese groups, and no differences in the pharmacokinetic profile have been identified on exposure to Buccolam.

No dose adjustment is warranted.

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

BUCCOLAM 2.5 mg oromucosal solution

18 months

BUCCOLAM 5 mg, 7.5 mg, 10 mg oromucosal solution

2 years

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.

| Strength | Volume of solution | Syringe volume | Age range | Label colour |
|----------|--------------------|----------------|-----------------------|--------------|
| 2.5 mg | 0.5 ml | 1 ml | 3 months to < 1 year | Yellow |
| 5 mg | 1 ml | 3 ml | 1 year to < 5 years | Blue |
| 7.5 mg | 1.5 ml | 3 ml | 5 years to < 10 years | Purple |
| 10 mg | 2 ml | 3 ml | 10 years to adults | Orange |

BUCCOLAM is available in two pack sizes:

- Cartons containing 2 pre-filled syringes.
- Cartons containing 4 pre-filled syringes.

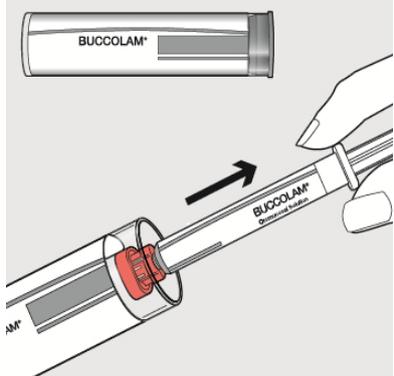
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

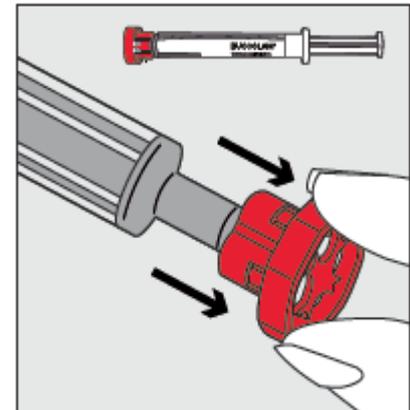
Administration of BUCCOLAM

BUCCOLAM is not for intravenous use.

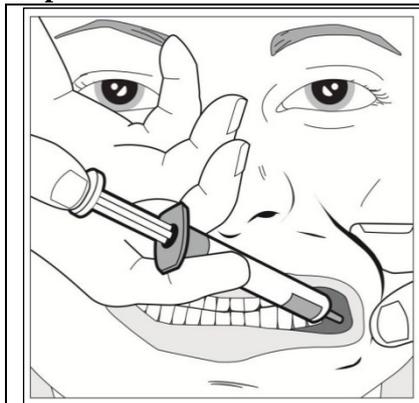
Step 1

| | |
|---|--|
|  | <p>Hold the plastic tube and pull the cap off. Take the syringe out of the tube.</p> |
|---|--|

Step 2

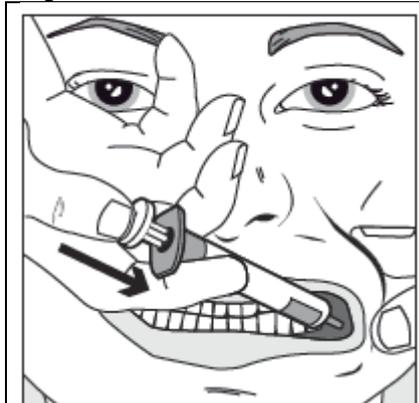
| | |
|---|--|
|  | <p>Pull the red cap off the tip of the syringe and dispose of it safely.</p> |
|---|--|

Step 3



Using the finger and thumb gently pinch and pull back the patient's cheek. Put the tip of the syringe into the back of the space between the inside of the cheek and the lower gum.

Step 4



Slowly press the syringe plunger until the plunger stops.

The full amount of solution should be inserted slowly into the space between the gum and the cheek (buccal cavity).

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.

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

7. MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

BUCCOLAM 2.5 mg oromucosal solution

EU/1/11/709/001

EU/1/11/709/005

BUCCOLAM 5 mg oromucosal solution

EU/1/11/709/002

EU/1/11/709/006

BUCCOLAM 7.5 mg oromucosal solution

EU/1/11/709/003

EU/1/11/709/007

BUCCOLAM 10 mg oromucosal solution

EU/1/11/709/004

EU/1/11/709/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 2011

Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal 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**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí
Barcelona - Spain

neuraxpharm Arzneimittel GmbH
Elisabeth-Selbert-Str. 23
40764 Langenfeld
Germany

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 5 mg, 7.5 mg and 10 mg:

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (2.5 mg/0.5 ml) containing 2 prefilled syringes

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
2 pre-filled oral syringes

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/005

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (2.5 mg/0.5 ml) containing 4 prefilled syringes

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

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Plastic Tube Label 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. NAME OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

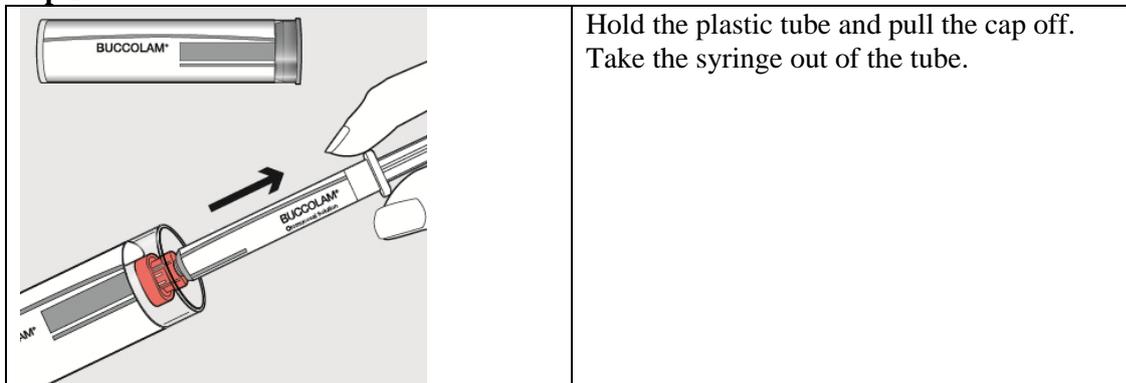
For oromucosal use only
Remove the oral syringe cap before use
Keep the oral syringe in the protective plastic tube
 Open Here

How to give this medicine

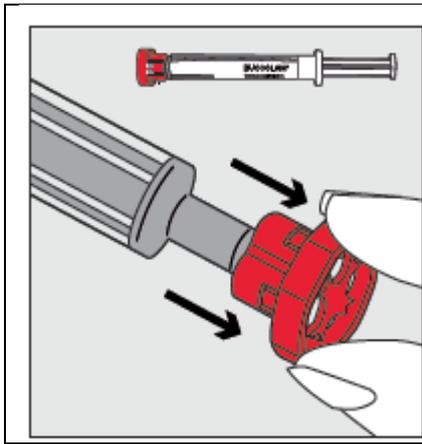
Buccolam must not be injected. Do not attach a needle to the syringe

The dose is the full contents of one syringe. Do not give more than one dose

Step 1

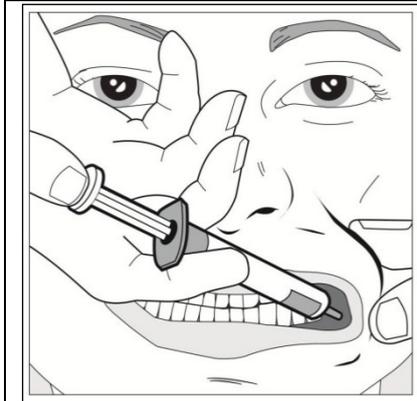


Step 2



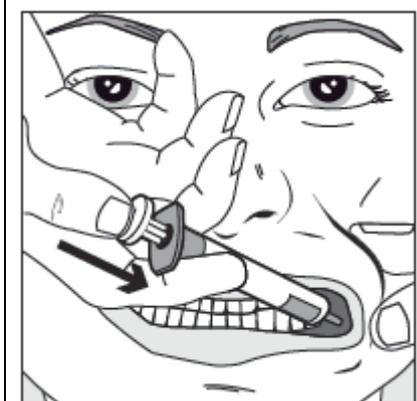
Pull the red cap off the tip of the syringe and dispose of it safely.

Step 3



Using the finger and thumb gently pinch and pull back the child's cheek. Put the tip of the syringe into the back of the space between the inside of the cheek and the lower gum.

Step 4



Slowly press the syringe plunger until the plunger stops.

The full amount of solution should be inserted slowly into the space between the gum and the cheek (buccal cavity).

If prescribed by your doctor (for larger volumes and/or smaller patients), you can give approximately half the dose slowly into one side of the mouth, then into the other side of the child's mouth.

When to call an ambulance

ALWAYS follow the treatment advice provided by the patient's doctor or as explained by a healthcare professional. If in any doubt, call for immediate medical help if:

- The seizure does not stop within 10 minutes
- You're unable to empty the syringe or you spill some of the contents
- The child's breathing slows down or stops e.g. slow or shallow breathing or blue lips
- You observe signs of a heart attack which may include chest pain or pain that spreads to the neck and shoulders and down the left arm
- The child is sick (vomits) and the seizure does not stop within 10 minutes
- You give too much BUCCOLAM and there are signs of overdose which include:
 - Drowsiness, tiredness, fatigue
 - Confusion or feeling disorientated
 - Absence of knee reflex or a response to a pinch
 - Breathing difficulties (slow or shallow breathing)
 - Low blood pressure (giddiness and feeling faint)
 - Coma

Keep the syringe to show to the ambulance staff or doctor.

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 2.5 mg/0.5 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BUCCOLAM 2.5 mg oromucosal solution
midazolam
For children aged 3 months to less than 1 year
For oromucosal use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mg

6. OTHER

Single use only
Remove the oral syringe cap before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (5 mg/1 ml) containing 2 prefilled syringes

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
2 pre-filled oral syringes

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/006

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (5 mg/1 ml) containing 4 prefilled syringes

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

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Plastic Tube Label 5 mg /1 ml

1. NAME OF THE MEDICINAL PRODUCT

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

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

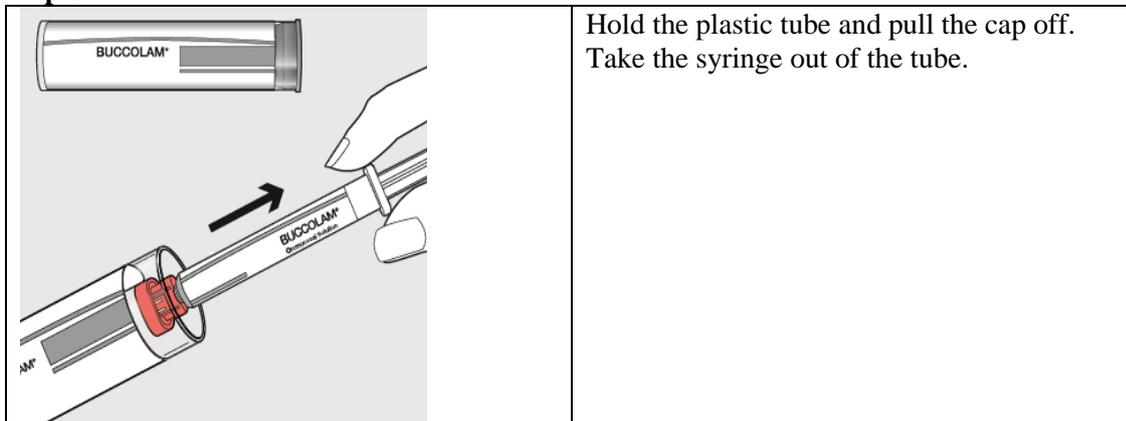
For oromucosal use only
Remove the oral syringe cap before use
Keep the oral syringe in the protective plastic tube
 Open Here

How to give this medicine

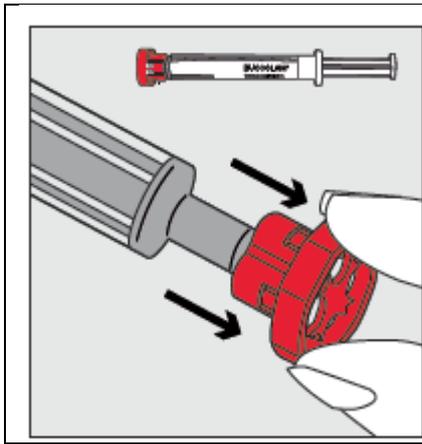
Buccolam must not be injected. Do not attach a needle to the syringe

The dose is the full contents of one syringe. Do not give more than one dose

Step 1

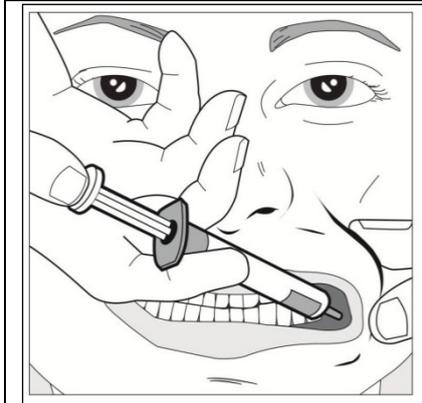


Step 2



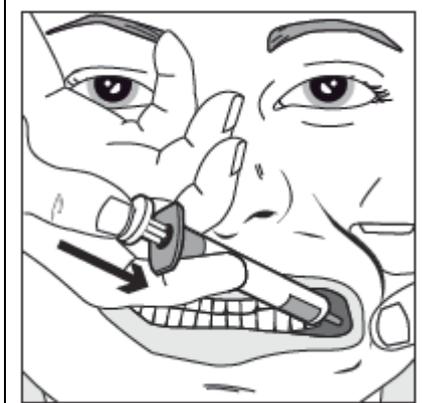
Pull the red cap off the tip of the syringe and dispose of it safely.

Step 3



Using the finger and thumb gently pinch and pull back the child's cheek. Put the tip of the syringe into the back of the space between the inside of the cheek and the lower gum.

Step 4



Slowly press the syringe plunger until the plunger stops.

The full amount of solution should be inserted slowly into the space between the gum and the cheek (buccal cavity).

If prescribed by your doctor (for larger volumes and/or smaller patients), you can give approximately half the dose slowly into one side of the mouth, then into the other side of the child's mouth.

When to call an ambulance

ALWAYS follow the treatment advice provided by the patient's doctor or as explained by a healthcare professional. If in any doubt, call for immediate medical help if:

- The seizure does not stop within 10 minutes
- You're unable to empty the syringe or you spill some of the contents
- The child's breathing slows down or stops e.g. slow or shallow breathing or blue lips
- You observe signs of a heart attack which may include chest pain or pain that spreads to the neck and shoulders and down the left arm
- The child is sick (vomits) and the seizure does not stop within 10 minutes
- You give too much BUCCOLAM and there are signs of overdose which include:
 - Drowsiness, tiredness, fatigue
 - Confusion or feeling disorientated
 - Absence of knee reflex or a response to a pinch
 - Breathing difficulties (slow or shallow breathing)
 - Low blood pressure (giddiness and feeling faint)
 - Coma

Keep the syringe to show to the ambulance staff or doctor.

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 5 mg/1 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BUCCOLAM 5 mg oromucosal solution
midazolam

For children aged 1 year to less than 5 years
For oromucosal use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg

6. OTHER

Single use only.
Remove the oral syringe cap before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (7.5 mg/1.5 ml) containg 2 prefilled syringes

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
2 pre-filled oral syringes

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/007

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (7.5 mg/1.5 ml) containing 4 prefilled syringes

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

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/003

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Plastic Tube Label 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. NAME OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

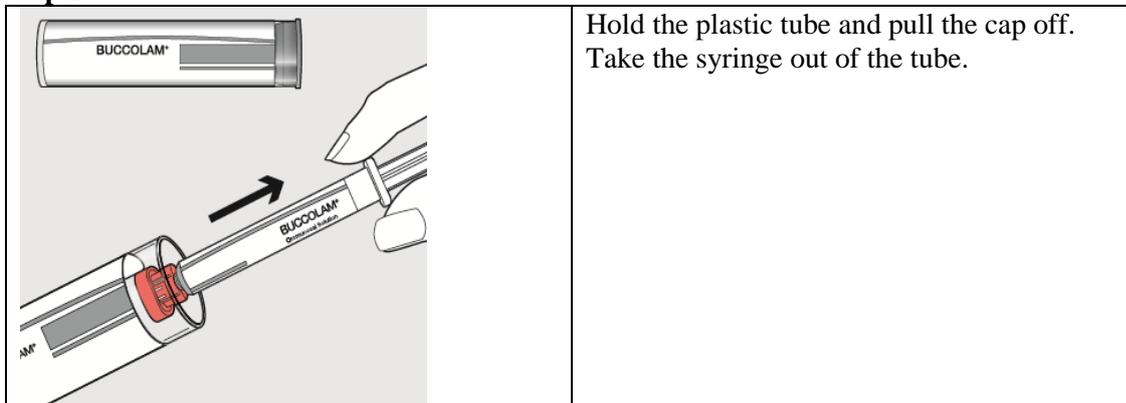
For oromucosal use only
Remove the oral syringe cap before use
Keep the oral syringe in the protective plastic tube
 Open Here

How to give this medicine

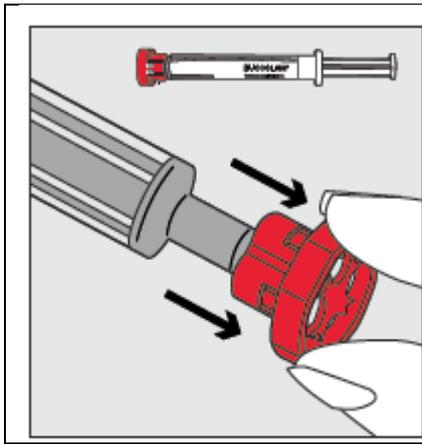
Buccolam must not be injected. Do not attach a needle to the syringe

The dose is the full contents of one syringe. Do not give more than one dose

Step 1

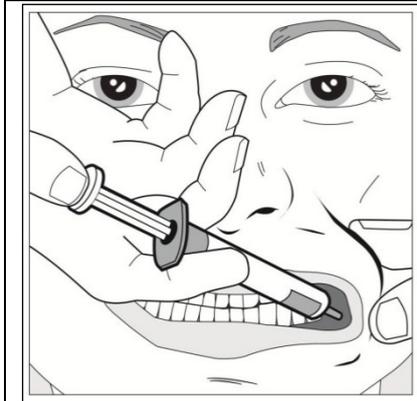


Step 2



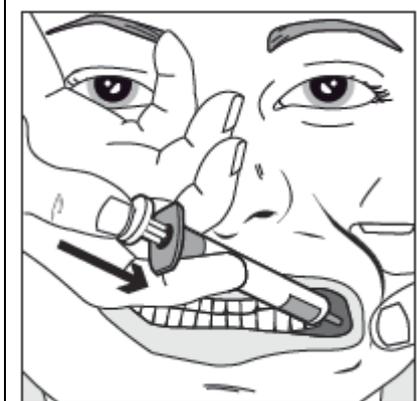
Pull the red cap off the tip of the syringe and dispose of it safely.

Step 3



Using the finger and thumb gently pinch and pull back the child's cheek. Put the tip of the syringe into the back of the space between the inside of the cheek and the lower gum.

Step 4



Slowly press the syringe plunger until the plunger stops.

The full amount of solution should be inserted slowly into the space between the gum and the cheek (buccal cavity).

If prescribed by your doctor (for larger volumes and/or smaller patients), you can give approximately half the dose slowly into one side of the mouth, then into the other side of the child's mouth.

When to call an ambulance

ALWAYS follow the treatment advice provided by the patient's doctor or as explained by a healthcare professional. If in any doubt, call for immediate medical help if:

- The seizure does not stop within 10 minutes
- You're unable to empty the syringe or you spill some of the contents
- The child's breathing slows down or stops e.g. slow or shallow breathing or blue lips
- You observe signs of a heart attack which may include chest pain or pain that spreads to the neck and shoulders and down the left arm
- The child is sick (vomits) and the seizure does not stop within 10 minutes
- You give too much BUCCOLAM and there are signs of overdose which include:
 - Drowsiness, tiredness, fatigue
 - Confusion or feeling disorientated
 - Absence of knee reflex or a response to a pinch
 - Breathing difficulties (slow or shallow breathing)
 - Low blood pressure (giddiness and feeling faint)
 - Coma

Keep the syringe to show to the ambulance staff or doctor.

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 7.5 mg/1.5 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BUCCOLAM 7.5 mg oromucosal solution
midazolam
For children aged 5 years to less than 10 years
For oromucosal use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7.5 mg

6. OTHER

Single use only
Remove the oral syringe cap before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (10 mg/2 ml) containing 2 prefilled syringes

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 10 mg oromucosal solution
midazolam
For children aged 10 years to adults

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
2 pre-filled oral syringes

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/008

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (10 mg/2 ml) containing 4 prefilled syringes

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 10 mg oromucosal solution
midazolam
For children aged 10 years to adults

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

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 WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/709/004

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BUCCOLAM 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Plastic Tube Label 10 mg /2 ml

1. NAME OF THE MEDICINAL PRODUCT

BUCCOLAM 10 mg oromucosal solution
midazolam
For children aged 10 years to adults

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

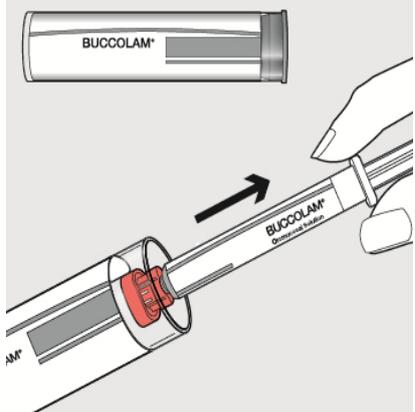
For oromucosal use only
Remove the oral syringe cap before use
Keep the oral syringe in the protective plastic tube
 Open Here

How to give this medicine

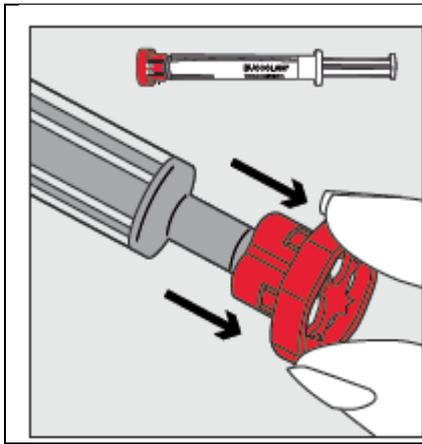
Buccolam must not be injected. Do not attach a needle to the syringe

The dose is the full contents of one syringe. Do not give more than one dose

Step 1

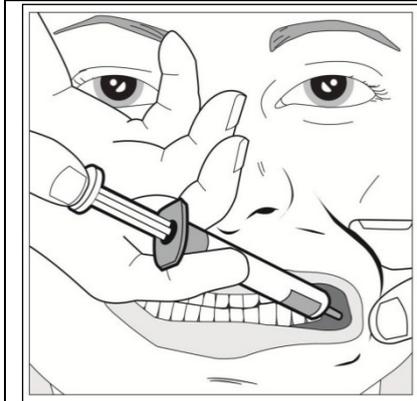
| | |
|---|--|
|  | <p>Hold the plastic tube and pull the cap off. Take the syringe out of the tube.</p> |
|---|--|

Step 2



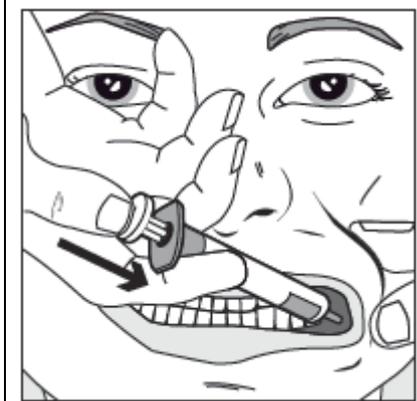
Pull the red cap off the tip of the syringe and dispose of it safely.

Step 3



Using the finger and thumb gently pinch and pull back the patient's cheek. Put the tip of the syringe into the back of the space between the inside of the cheek and the lower gum.

Step 4



Slowly press the syringe plunger until the plunger stops.

The full amount of solution should be inserted slowly into the space between the gum and the cheek (buccal cavity).

If prescribed by your doctor (for larger volumes and/or smaller patients), you can give approximately half the dose slowly into one side of the mouth, then into the other side of the patient's mouth.

When to call an ambulance

ALWAYS follow the treatment advice provided by the patient's doctor or as explained by a healthcare professional. If in any doubt, call for immediate medical help if:

- The seizure does not stop within 10 minutes
- You're unable to empty the syringe or you spill some of the contents
- The patient's breathing slows down or stops e.g. slow or shallow breathing or blue lips
- You observe signs of a heart attack which may include chest pain or pain that spreads to the neck and shoulders and down the left arm
- The patient is sick (vomits) and the seizure does not stop within 10 minutes
- You give too much BUCCOLAM and there are signs of overdose which include:
 - Drowsiness, tiredness, fatigue
 - Confusion or feeling disorientated
 - Absence of knee reflex or a response to a pinch
 - Breathing difficulties (slow or shallow breathing)
 - Low blood pressure (giddiness and feeling faint)
 - Coma

Keep the syringe to show to the ambulance staff or doctor.

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Plastic oral syringe 10 mg/2 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BUCCOLAM 10 mg oromucosal solution
midazolam
For children aged 10 years to adults
For oromucosal use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg

6. OTHER

Single use only.
Remove the oral syringe cap before use.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

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

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

**BUCCOLAM 10 mg oromucosal solution
For children aged 10 years to adults**

Midazolam

Read all of this leaflet carefully, before you start giving this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of the patient for whom this medicine has been prescribed.
- If you see any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What BUCCOLAM is and what it is used for
2. What you need to know before you give BUCCOLAM
3. How to give BUCCOLAM
4. Possible side effects
5. How to store BUCCOLAM
6. Contents of the pack and other information

1. What BUCCOLAM is and what it is used for

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

BUCCOLAM is used to stop a sudden, prolonged, convulsive, seizure in infants from 3 months to adults.

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

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

2. What you need to know before you give BUCCOLAM

Do not give BUCCOLAM if the patient has:

- An allergy to midazolam, benzodiazepines (such as diazepam) or any of the other ingredients of this medicine (listed in section 6)
- A disease of the nerves and muscles causing muscle weakness (myasthenia gravis)
- Severe 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.

Warnings and precautions

Children:

Talk to your doctor or pharmacist before giving BUCCOLAM if the patient has:

- A kidney, liver or heart condition
- A lung condition that causes difficulty breathing on a regular basis.

Adults:

Talk to your doctor or pharmacist before you are given BUCCOLAM if:

- You are over 60 years of age.
- You have a long-term illness (such as breathing problems or kidney, liver or heart problems).
- You are debilitated (have an illness that makes you feel very weak, run down and short of energy).

This medicine may cause people to forget what happened after they have been given it. Patients should be observed carefully after being given the medicine.

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

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.

Elderly: The elderly are more sensitive to the effects of benzodiazepines.

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

Other medicines and BUCCOLAM

Tell your doctor or pharmacist if the patient is taking, or has recently taken, or might take any other medicines. If you have any doubt about whether any medicine 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.

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, posaconazole
- 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

- hypnotics (sleep inducing medicines)
- sedative antidepressants (medicines used to treat depression that make you sleepy)
- sedatives (medicines that relax you)
- anaesthetics (for pain relief)
- antihistamines (to treat allergies).

The effects of BUCCOLAM may be reduced by medicines such as:

- rifampicin (used to treat tuberculosis)
- xanthines (used to treat asthma)
- St John's Wort (a herbal medicine). This should be avoided in patients taking BUCCOLAM.

BUCCOLAM may increase the effect of some muscle relaxants e.g. baclofen (causing increased drowsiness). This medicine may also stop some other medicines from working as well, e.g. levodopa (used to treat Parkinson's disease).

Talk to your doctor or pharmacist about medicines the patient should avoid whilst taking BUCCOLAM.

BUCCOLAM with food and drink

The patient must not drink alcohol while taking BUCCOLAM. Alcohol may increase the sedative effects of this medicine and make them very sleepy.

The patient must not drink grapefruit juice while taking BUCCOLAM. Grapefruit juice may increase the sedative effects of this medicine and make them very sleepy.

Pregnancy

If the patient who will be given this medicine is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, ask a doctor for advice before taking this medicine.

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

Breast-feeding

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

Driving and using machines

BUCCOLAM may make the patient sleepy, forgetful or affect their concentration and co-ordination. This may affect their performance at skilled tasks such as driving, riding a bicycle, or using machines.

After receiving this medicine, 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.

BUCCOLAM contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per oral syringe, that is to say essentially 'sodium-free'.

3. How to give BUCCOLAM

Always give this medicine exactly as a doctor has told you. Check with a doctor or pharmacist if you are not sure.

Dosage

The doctor will prescribe the appropriate dose of BUCCOLAM the patient needs, generally according to the patient age. The different doses each have a different colour, which is shown on the carton, the tube and the syringe containing the medicine.

Depending on age, the patient will have received one of the following doses, in specifically colour labelled packaging:

3 months to less than 1 year: 2.5 mg - yellow labelled packaging

1 year to less than 5 years: 5 mg - blue labelled packaging

5 years to less than 10 years: 7.5 mg - purple labelled packaging

10 years to adults: 10 mg - orange labelled packaging

The dose is the full contents of one oral syringe. Do not give more than one dose.

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.

Preparing to give this medicine

If the patient is having a seizure, allow their body to move freely, do not try to restrain them. Only move them if they are in danger from, for example, deep water, fire or sharp objects.

Support the patient's head with something soft, such as a cushion or your lap.

Check that the medicine is the correct dose for the patient, according to their age.

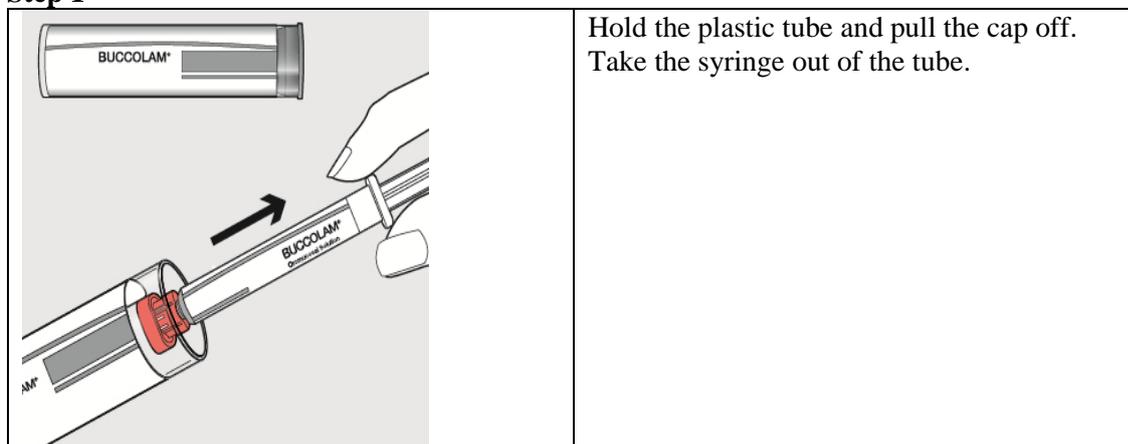
How to give this medicine

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.

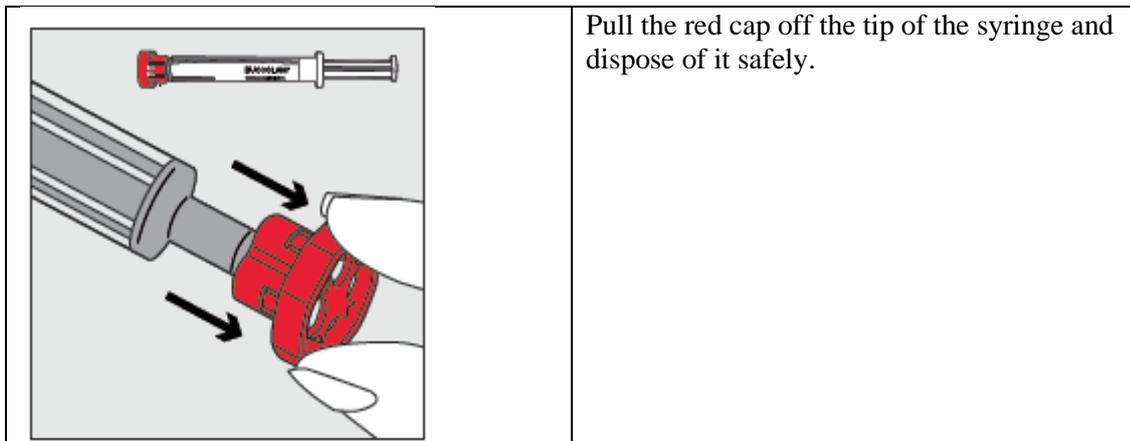
The information on how to give this medicine is also shown on the tube label.

Buccolam must not be injected. Do not attach a needle to the syringe

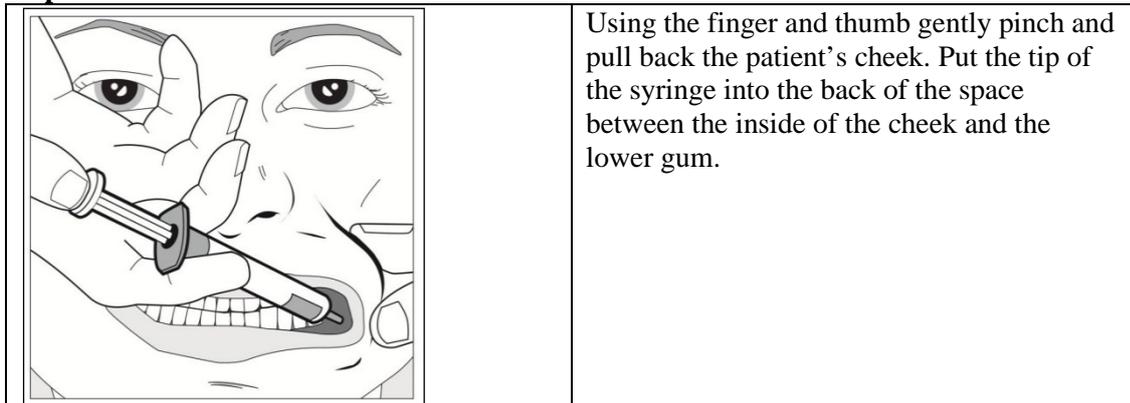
Step 1



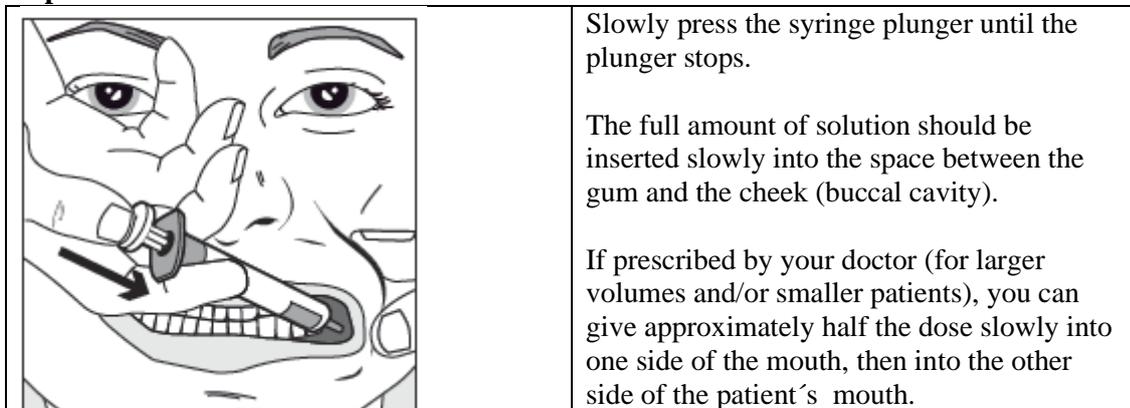
Step 2



Step 3



Step 4



When to call an ambulance

ALWAYS follow the treatment advice provided by the patient's doctor or as explained by a healthcare professional. If in any doubt, call for immediate medical help if:

- The seizure does not stop within 10 minutes
- You're unable to empty the syringe or you spill some of the contents
- The patient's breathing slows down or stops e.g. slow or shallow breathing or blue lips
- You observe signs of a heart attack which may include chest pain or pain that spreads to the neck and shoulders and down the left arm
- The patient is sick (vomits) and the seizure does not stop within 10 minutes
- You give too much BUCCOLAM and there are signs of overdose which include:
 - Drowsiness, tiredness, fatigue
 - Confusion or feeling disorientated

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

Keep the syringe to show to the ambulance staff or doctor.

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

If the patient is sick (vomits)

- Do not give the patient another dose of BUCCOLAM.
- If the seizure does not stop within 10 minutes, call an ambulance.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Seek medical advice immediately or telephone for an ambulance if the patient experiences the following:

- Severe breathing difficulties e.g. slow or shallow breathing or blue lips. In very rare cases breathing might stop.
- Heart attack. Signs may include chest pain which may spread to the patient's neck and shoulders and down their left arm.
- Swelling of the face, lips, tongue or throat which makes it difficult to swallow or breathe, or a pale skin, a weak and rapid pulse, or feeling of loss of consciousness. You may be having a serious allergic reaction.

Other side effects

If the patient gets any side effects, talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Common side effects (may affect up to 1 in 10 people):

- Feeling and being sick
- Sleepiness or losing consciousness

Uncommon side effects (may affect up to 1 in 100 people):

- Rash, hives (lumpy rash), itchiness

Very rare side effects (may affect up to 1 in 10,000 people):

- Agitation, restlessness, hostility, rage or aggression, excitement, confusion, euphoria (an excessive feeling of happiness or excitement), or hallucinations (seeing and possibly hearing things that are not really there)
- Muscle spasms and muscle tremors (shaking of your muscles that you cannot control)
- Reduced alertness
- Headache
- Dizziness
- Difficulty co-ordinating muscles
- Fits (convulsions)
- Temporary memory loss. How long this lasts depends on how much BUCCOLAM was given..

- Low blood pressure, slow heart rate, or redness of the face and neck (flushing)
- Laryngospasm (tightening of the vocal cords causing difficult and noisy breathing)
- Constipation
- Dry mouth
- Tiredness
- Hiccups

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BUCCOLAM

Keep this medicine out of the sight and reach of children.

Do not give this medicine 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.

Do not use this medicine if the packaging has been opened or damaged.

Disposal of oral syringes

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What BUCCOLAM contains

- The active substance is midazolam
- Each 2.5 mg pre-filled oral syringe contains 2.5 mg midazolam (as hydrochloride) in 0.5 ml solution.
- Each 5 mg pre-filled oral syringe contains 5 mg midazolam (as hydrochloride) in 1 ml solution.
- Each 7.5 mg pre-filled oral syringe contains 7.5 mg midazolam (as hydrochloride) in 1.5 ml solution.
- Each 10 mg pre-filled oral syringe contains 10 mg midazolam (as hydrochloride) in 2 ml solution.

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

What BUCCOLAM looks like and contents of the pack

3 months to less than 1 year: 2.5 mg - yellow labelled packaging
 1 year to less than 5 years: 5 mg - blue labelled packaging
 5 years to less than 10 years: 7.5 mg - purple labelled packaging
 10 years to adults: 10 mg - orange labelled packaging

BUCCOLAM oromucosal solution is a clear colourless to yellowish liquid. It is supplied in an amber coloured pre-filled, single-use oral syringe. Each oral syringe is individually packed in a protective plastic tube. BUCCOLAM is available in cartons containing 2 and 4 pre-filled oral syringes/tubes (of the same dose).

Not all pack sizes may be marketed.

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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.