Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Midazolam Rowa 2.5 mg oromucosal solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Midazolam Rowa 2.5 mg oromucosal solution
Each pre-filled oral syringe contains midazolam hydrochloride equivalent to 2.5 mg midazolam in 0.5 ml solution.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oromucosal solution Clear 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.

Midazolam Rowa 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 Midazolam Rowa under healthcare professional supervision should be considered prior to starting treatment with Midazolam Rowa. This administration may be performed in the absence of a seizure.

Special populations

Renal impairment
No dose adjustment is required, however, Midazolam Rowa 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).

Midazolam Rowa is contraindicated in patients with severe hepatic impairment (see section 4.3).

Elderly

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

Method of administration

Midazolam Rowa 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.

Midazolam Rowa 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 Midazolam Rowa 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 otherbenzodiazepines

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

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.

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: ≥ 1/100 to < 1/10 Uncommon: ≥ 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
Immune system disorders	Not known: anaphylactic 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**, dyspnoea**, 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**

***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 HPRA Pharmacovigilance, website: www.hpra.ie

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 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.

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	$AUC_{0\text{-}inf}$ (ng.h/ml)	168	98
		C_{max} (ng/ml)	104	46
5 mg	1 yr < 5 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	242	116
		C_{max} (ng/ml)	148	62
7.5 mg	5 yrs <10 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	254	136
		C_{max} (ng/ml)	140	60
10 mg	10 yrs < 18 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	189	96
		C_{max} (ng/ml)	87	44
1. mg	>18 yrs	AUC0-inf (ng.h/ml) (n=22)	259	62
		Cmax (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 paediatrics 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 midazolam.

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
Purified water
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

24 months

6.4 Special precautions for storage

Keep the oral syringe in the protective plastic tube.
Do not store above 30ºC

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 < 18 years	Orange

MidazolamRowa is available in cartons containing 2 and 4 pre-filled oral syringes.

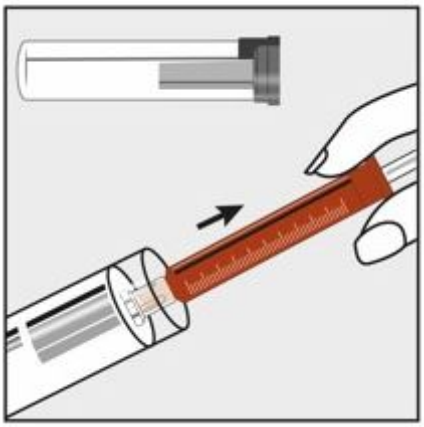
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

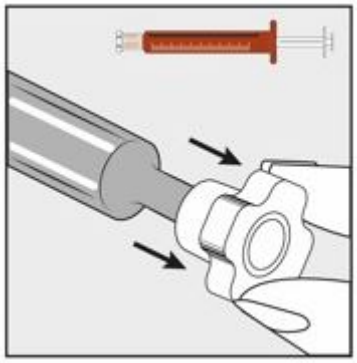
Administration of Midazolam Rowa

Midazolam Rowa is not for intravenous use.

Step 1

	Hold the plastic tube, break the seal at one end and pull the cap off. Take the syringe out of the tube.

Step 2

	Pull the transparent 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 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

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 2021
Date of last renewal: 6th October 2025

10 DATE OF REVISION OF THE TEXT

April 2025