B. PACKAGE LEAFLET

Package leaflet: Information for the user

Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe
Midazolam 2 mg/ml solution for injection/infusion in pre-filled syringe

midazolam

For use in adults

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Midazolam is and what it is used for

Midazolam belongs to a group of medicines known as benzodiazepines. It is a short-acting medicine that is used to induce sedation (a very relaxed state of calm, drowsiness or sleep) and relieves anxiety and muscle tension.

This medicine is used for:
- sedation of adults in intensive care units

2. What you need to know before you are given Midazolam

You must NOT be given Midazolam
- if you are allergic to midazolam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other benzodiazepine medicines, such as diazepam or nitrazepam.
- if you have severe breathing problems.

You must not be given Midazolam if any of the above apply to you. If you are not sure, talk to your doctor before you are given this medicine.

Warnings and precautions

Administration of midazolam may depress myocardial contractility (ability of heart muscle to contract) and cause apnoea (pauses in breathing). Severe cardio respiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory and/or cardiac arrest. To avoid such incidents, the injection should be given slowly and the dose should be as low as possible.

Paradoxical reactions and anterograde amnesia (loss of memory for recent events) have been reported to occur with midazolam (see section 4. Possible side effects).

Adults
Talk to your doctor before you are given Midazolam, 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)
- you have a condition called 'sleep apnoea syndrome' (where your breathing stops when you are asleep), so you may be closely monitored
- you have myasthenia gravis (a neuromuscular disease causing muscle weakness)
- you regularly drink large amounts of alcohol or you have had problems with alcohol use in the past. Alcohol can increase the effects of Midazolam, possibly leading to severe sedation that could result in coma or death
- you regularly take recreational drugs or you have had problems with drug use in the past.

If any of the above apply to you, or if you are not sure, talk to your doctor or nurse before you are given Midazolam.

Other medicines and Midazolam
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal medicines.

This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- tranquilisers (for anxiety or to help you sleep)
- hypnotics (medicines to make you sleep)
- sedatives (to make you feel calm or sleepy)
- antidepressants (medicines for depression)
- narcotic analgesics (very strong pain killers)
- antihistamines (used to treat allergies)
- medicines to treat fungal infections (ketoconazole, voriconazole, fluconazole, itraconazole, posaconazole)
- macrolide antibiotics (such as erythromycin or clarithromycin)
- diltiazem (used to treat high blood pressure)
- medicines for HIV called protease inhibitors (such as saquinavir)
- medicines for hepatitis C (protease inhibitors such as boceprevir and telaprevir)
- atorvastatin (used to treat high cholesterol)
- rifampicin (used to treat mycobacterial infections such as tuberculosis)
- ticagrelor (used to prevent heart attack)
- the herbal medicine St John's Wort.

If any of the above apply to you, or if you are not sure, talk to your doctor or nurse before you are given Midazolam.

Operations
If you are going to have an anaesthetic for an operation or for dental treatment (including inhaled anaesthetics that you breathe in), it is important to tell your doctor or dentist that you have been given Midazolam.

Midazolam with alcohol
Do not drink alcohol if you have been given Midazolam. This is because alcohol can increase the sedative effect of Midazolam and may cause problems with your breathing.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine. Your doctor will decide if this medicine is suitable for you.

Midazolam may harm your unborn baby when used in early pregnancy. When high doses are administered during late pregnancy, labour or caesarean section, you might have an inhalation risk and your baby might have an irregular heartbeat, state of low muscle tone (hypotonia), feeding difficulties, a low body temperature and difficulty in breathing. With prolonged administration during late pregnancy, your baby may develop a physical dependence and risk of withdrawal symptoms after birth.

Do not breast-feed for 24 hours after being given Midazolam. This is because Midazolam may pass into your breast milk.

Driving and using machines
- Midazolam may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving or using machines.
- Do not drive or use machinery until you are completely recovered. Your doctor should advise you when you can start these again.
- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
  - However, you would not be committing an offence if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
    - It was not affecting your ability to drive safely.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

- Lack of sleep or alcohol consumption may further impair your alertness.
- You should always be taken home by a responsible adult after your treatment.

Midazolam contains sodium
This medicinal product contains 157.36 mg sodium (main component of cooking/table salt) in each pre-filled syringe. This is equivalent to 7.9% of the maximum daily dietary intake of sodium for an adult.

3. How to use Midazolam

Midazolam should be given only by experienced healthcare professionals. It should be given in a place (hospital, clinic or surgery) equipped to monitor and support the patient's breathing, heart and circulation (cardiovascular function) and recognise the signs of and manage the expected side effects of anaesthesia.

Usual adult dose
Your doctor will decide on a suitable dose for you. The dose you are given will depend on why you are being treated and the type of sedation needed. Your weight, age, your state of health, how you respond to Midazolam and whether other medicines are needed at the same time will also influence the dose that you are given.

If you need strong painkillers, you will be given these first and then be given Midazolam. The dose will be adjusted specially for you.

Children
Midazolam is not recommended for use in children due to the total amount of midazolam contained in the pre-filled syringes.

Method of administration
Midazolam may be given to you in one of two different ways:
- by slow injection into a vein (intravenous injection)
- through a tube into one of your veins (intravenous infusion).

You should always be taken home by a responsible adult after your treatment.

If you receive more Midazolam than you should
Your medicine will be given to you by a doctor or nurse. If you are accidentally given too much Midazolam you may:
- feel drowsy
- lose your co-ordination (ataxia) and reflexes
- have problems with your speech (dysarthria)
- have involuntary eye movements (nystagmus)
- develop low blood pressure (hypotension)
- stop breathing (apnoea) and suffer cardiorespiratory depression (slowed or stopped breathing and heart beat) and coma.

If you stop using Midazolam
If you receive long term treatment with Midazolam (are given the medicine for a long time) you may:
- become tolerant to midazolam. The medicine becomes less effective and does not work as well for you
- become dependent upon this medicine and get withdrawal symptoms (see below).

The following effects have been seen with midazolam use, particularly in the elderly; restlessness, agitation, irritability, involuntary movements, hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations (seeing and possibly hearing things that are not really there), psychoses (losing contact with reality), inappropriate behaviour, excitement and assault (these are also known as paradoxical reactions, which are outcomes that are opposite to the effects normally expected for the drug). If you experience these, your doctor will consider stopping Midazolam treatment.

Your doctor will reduce your dose gradually to avoid these effects happening to you.

Withdrawal symptoms:
Benzodiazepine medicines, like Midazolam, may make you dependent if used for a long time (for instance in intensive care). This means that if you stop treatment suddenly, or lower the dose too quickly, you may get withdrawal symptoms. The symptoms can include:
- headache
- diarrhoea
- muscle pain
- feeling very worried (anxious), tense, restless, confused or bad-tempered (irritable)
- problems with sleeping
- mood changes
- hallucinations (seeing and possibly hearing things that are not there)
- fits (convulsions).

In severe cases of withdrawal, the following can occur: a feeling of losing contact with reality,

numbness and tingling of the extremities (e.g. hands and feet), feeling sensitive to light, noise and touch.

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

4. Possible side effects

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

The following side effects have been reported (frequency not known).

Stop having Midazolam and see a doctor straight away if you notice any of the following side effects. They can be life-threatening and you may need urgent medical treatment:
- anaphylactic shock (a life-threatening allergic reaction). Signs may include a sudden rash, itching or lumpy rash (hives) and swelling of the face, lips, tongue or other parts of the body. You may also have shortness of breath, wheezing or trouble breathing, or a pale skin, a weak and rapid pulse, or feeling of loss of consciousness. Additionally, you may experience chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.
- heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm
- breathing problems or complications (sometimes causing the breathing to stop)
- choking and sudden blockage of the airway (laryngospasm).

Life-threatening side effects are more likely to occur in adults over 60 years of age and those who already have breathing difficulties or heart problems, particularly if the injection is given too fast or at a high dose.

Other possible side effects (frequency not known)

Not known (cannot be estimated from the available data)
Immune system problems:
- general allergic reactions (skin reactions, heart and blood system reactions, wheezing)

Effects on behaviour:
- restlessness, agitation, irritability
- nervousness, anxiety
- hostility, rage or aggression
- excitement
- hyperactivity
- changes in libido
- inappropriate behaviour.

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

Mental and nervous system problems:
- confusion, disorientation
- emotional and mood disturbances
- involuntary movements
- nightmares, abnormal dreams
- hallucinations (seeing and possibly hearing things that are not really there)
- psychoses (losing contact with reality)
- drowsiness and prolonged sedation
- reduced alertness

- headache
- dizziness
- difficulty co-ordinating muscles
- temporary memory loss. How long this lasts depends on how much Midazolam you were given. You may experience this after your treatment. In isolated cases this has been prolonged (lasted for a long time)
- drug dependence, abuse.

Heart and circulation problems:
- low blood pressure
- slow heart rate
- redness of the face and neck (flushing), fainting or headache.

Breathing problems:
- shortness of breath
- hiccup.

Stomach, gut and mouth problems:
- feeling sick or being sick
- constipation
- dry mouth.

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

Injection site problems:
- redness
- swelling of the skin
- blood clots or pain at the injection site.

Injury:
- patients taking benzodiazepine medicines are at risk of falling and breaking bones. This risk is increased in the elderly and those taking other sedatives (including alcohol).

General:
- tiredness (fatigue).

Elderly patients:
- life-threatening side effects are more likely to occur in adults over 60 years of age and those who already have breathing difficulties or heart problems, particularly when the injection is given too quickly or at a high dose.

Patients with severe kidney disease:
- patients with severe kidney disease are more likely to experience side effects.

If any of the side effects become serious or troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Midazolam

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

Do not use this medicine after the expiry date which is stated on the carton, foil or pre-filled syringe labels after EXP. The expiry date refers to the last day of that month.

Keep the pre-filled syringe in the outer carton, in order to protect from light.

Your doctor or pharmacist is responsible for storing Midazolam. They are also responsible for disposing of any unused Midazolam correctly.

6. Contents of the pack and other information

What Midazolam contains
- The active substance is midazolam.

Midazolam 1 mg/ml:
Each ml of the solution for injection/infusion contains 1 mg midazolam.
Each pre-filled syringe of 50 ml contains 50 mg midazolam.

Midazolam 2 mg/ml:
Each ml of the solution for injection/infusion contains 2 mg midazolam.
Each pre-filled syringe of 50 ml contains 100 mg midazolam.

- The other ingredients are sodium chloride, hydrochloric acid 0.5% (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection.

What Midazolam looks like and contents of the pack
Midazolam is a clear, colourless to viscous solution for injection/infusion.
Midazolam is available in a pack containing one blister with one pre-filled syringe containing 50 ml solution for injection/infusion.

Marketing Authorisation Holder
Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

Manufacturer
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124 Fabricii Street
400632, Cluj-Napoca
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This medicinal product is authorised in the Member States of the EEA under the following names

Germany	Midazolam SUN
France	Midazolam SUN
Italy	Midazolam SUN
Poland	Midazolam SUN
Romania	Midazolam SUN
Spain	Midazolam SUN
United Kingdom	Midazolam

This leaflet was last revised in July 2023.

The following information is intended for healthcare professionals only:

INFORMATION FOR THE HEALTHCARE PROFESSIONALS

Please refer to the Summary of Product Characteristics for full prescribing information.

Posology and method of administration
Midazolam is a potent sedative active substance that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard doses are provided in the table below.

Additional details are provided in the text following the table.

Indication	Adults
Sedation in ICU	**i.v.** Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5 mg Maintenance dose: 0.03 - 0.2 mg/kg/h

Sedation in intensive care units

The desired level of sedation is reached by stepwise titration of midazolam followed by continuous infusion, according to the clinical need, physical status, age and concomitant medication.

Adults: i.v. loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted or hypothermic patients the loading dose should be reduced or omitted. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

I.V. maintenance dose: doses can range from 0.03 to 0.2 mg/kg/h. In hypovolaemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased. Midazolam 2 mg/ml should be used if higher doses are required.

When initiating an infusion with midazolam in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.

Use in special populations

Renal impairment: In patients with severe renal impairment (creatinine clearance below 30 ml/min) midazolam may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Midazolam should therefore be dosed carefully in this patient population and titrated for the desired effect. In patients with renal failure (creatinine clearance < 10 ml/min) the pharmacokinetics of unbound midazolam following a single i.v. dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive

care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population was considerably increased most likely due to accumulation of 1'-hydroxymidazolam glucuronide.

Hepatic impairment: hepatic impairment reduces the clearance of i.v. midazolam with a subsequent increase in terminal half-life. Therefore the clinical effects in patients with hepatic impairment may be stronger and prolonged. The required dose of midazolam may have to be reduced and proper monitoring of vital signs should be established.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

The use of PVC extension sets should be avoided. Where the use of PVC extension sets is unavoidable, their use should be limited to 24 hours.

Special precautions for storage
Keep the pre-filled syringe in the outer carton in order to protect from light.