Package leaflet: Information for the patient

Hypnovel® 10 mg/2 ml solution for injection
Hypnovel® 10 mg/5 ml solution for injection

Midazolam (as midazolam hydrochloride)

Read all of this leaflet carefully before you are given 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 nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT HYPNOVEL IS AND WHAT IT IS USED FOR

Hypnovel contains the active substance midazolam, which 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:
- Conscious sedation (an awake but very relaxed state of calm or drowsiness during a medical test or procedure) in adults and children.
- Sedation of adults and children, in intensive care units.
- Anaesthesia in adults, used alone or with other medicines.
- Premedication (medicine used to cause relaxation, calm and drowsiness before an anaesthetic) in adults and children.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN HYPNOVEL

You must not be given Hypnovel if:
- You are allergic (hypersensitive) to midazolam or any of the other ingredients of the medicine (listed in section 6).
- You are allergic to other benzodiazepine medicines, such as diazepam or nitrazepam.
- You have severe breathing problems and you are going to have Hypnovel for conscious sedation.

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

Warnings and precautions

Children and babies
If your child is going to be given this medicine:
- It is particularly important to tell your doctor or nurse if your child has cardiovascular disease (heart problems). Your child will be carefully monitored and the dose will be adjusted specially.
- Children must be carefully monitored. For infants and babies under 6 months this will include monitoring of breathing and oxygen levels.

Adults
Talk to your doctor or nurse before you are given Hypnovel 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 clinical effects of Hypnovel, possibly including 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.
- You are pregnant or think you may be pregnant (see 'Pregnancy and breast-feeding').

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

Other medicines and Hypnovel
Tell your doctor or nurse if you are taking, have recently taken or might start taking any other medicines. This includes 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 or antipsychotics (medicines for depression or schizophrenia)
- narcotic analgesics (very strong pain killers)
- cough medicines (such as ones containing codeine)
- antihistamines (used to treat allergies)
- medicines to treat fungal infections (ketoconazole, voriconazole, fluconazole, itraconazole, posaconazole)
- macrolide antibiotics (such as erythromycin, clarithromycin or roxithromycin)
- medicines used to treat high blood pressure and heart disease (such as dilitazem, verapamil and methyldopa)
- medicines for HIV (efavirenz or 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
- carbamazepine (used to treat epilepsy and bi-polar disorder)
- phenytoin (used to treat epilepsy)

- aprepitant (used to stop you feeling or being sick).

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

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 Hypnovel.

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

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

Hypnovel 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 Hypnovel. This is because Hypnovel may pass into your breast milk.

Driving and using machines
Hypnovel may make you sleepy, dizzy, 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.

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.

Important information about some of the ingredients of Hypnovel
Hypnovel is essentially ‘sodium free’ as it contains less than 1 mmol sodium (23 mg) per ampoule (small glass bottle).

3. HOW HYPNOVEL IS GIVEN

Hypnovel should be given only by experienced healthcare professionals (doctor or nurse). 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.

How much Hypnovel is given

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 Hypnovel 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 Hypnovel. Your doctor will decide on a suitable dose for you.

How Hypnovel is given
Hypnovel may be given to you in one of four different ways:
- by slow injection into a vein (intravenous injection)
- through a tube into one of your veins (intravenous infusion)
- by injection into a muscle (intramuscular injection)
- into your back passage (rectum).

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

Children and babies
- In infants and babies under 6 months of age Hypnovel is only recommended for sedation in intensive care units. The dose will be given gradually into a vein.
- Children 12 years and under will usually be given Hypnovel into a vein. When Hypnovel is used for premedication (to cause relaxation, calm and drowsiness before an anaesthetic) it may be given into the back passage (rectum).

If too much Hypnovel is given
Your medicine will be given to you by a doctor or nurse. If you are accidentally given too much Hypnovel 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.

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

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

The following effects have been seen with Hypnovel use particularly in children and the elderly; restlessness, agitation, irritability, involuntary movements, hyperactivity, nervousness, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations (seeing and possibly hearing things that are not really there), psychoses (losing contact with reality) and inappropriate behaviour (these reactions 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 Hypnovel treatment.

Withdrawal symptoms:
Benzodiazepine medicines, like Hypnovel, 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.

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 with this medicine (frequency not known).

Stop having Hypnovel 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
Immune system problems:
- general allergic reactions (skin reactions, heart and blood system reactions, wheezing).

Effects on behaviour:
- restlessness, agitation, irritability
- nervousness, anxiety
- hostility, anger, aggression or assault
- 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
- fits (convulsions) in premature infants and new-born babies
- temporary memory loss. How long this lasts depends on how much Hypnovel 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).

Unexpected reactions:
- unexpected (paradoxical) reactions such as restlessness, agitation, irritability, involuntary movements (including muscle tremor), hyperactivity, nervousness, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations (seeing and possibly hearing things that are not really there), psychoses (losing contact with reality) and inappropriate behaviour, excitement and assault have occurred with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. These reactions occur most commonly in children and the elderly.

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 or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE HYPNOVEL

Your doctor or pharmacist is responsible for storing Hypnovel. The storage details are as follows:

- 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 after EXP. The expiry date refers to the last day of that month.
- Keep ampoules (small glass bottle) in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Hypnovel contains
The active substance in **Hypnovel** is midazolam (as midazolam hydrochloride).

The other ingredients are sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

Hypnovel comes in two different strengths.

- **Hypnovel 10 mg/2 ml**. Each 1 ml of solution contains 5 mg (milligrams) of midazolam. Each ampoule (small glass bottle) contains 10 mg of midazolam (in 2 millilitres of solution).
- **Hypnovel 10 mg/5 ml**. Each 1 ml of solution contains 2 mg (milligrams) of midazolam. Each ampoule (small glass bottle) contains 10 mg of midazolam (in 5 millilitres of solution).

What Hypnovel looks like and contents of the pack
Hypnovel is a clear colourless liquid (‘solution for injection’). This liquid may be further diluted to make it weaker before it is given to you.

Hypnovel is supplied in clear glass ampoules in packs of 10.

Marketing Authorisation Holder
CHEPLAPHARM Arzneimittel GmbH
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17489 Greifswald

Germany

Manufacturer
CENEXI
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France

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The following information is intended for healthcare professionals only:
The tear-off portion above is intended for the patient

INFORMATION FOR HEALTHCARE PROFESSIONALS

Hypnovel® 10 mg/2 ml solution for injection
Hypnovel® 10 mg/5 ml solution for injection

Midazolam (as midazolam hydrochloride)

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

Presentation

Either 2 ml glass ampoules containing 10 mg/2 ml midazolam or 5 ml glass ampoules containing 10 mg/5 ml midazolam. The solution is clear and colourless. Excipients are sodium chloride, hydrochloric acid, sodium hydroxide solution and water for injections. Hypnovel 10 mg/2 ml, cartons of 10 ampoules. Hypnovel 10 mg/5 ml, cartons of 10 ampoules.

Important information about the excipients in Hypnovel.
Hypnovel is essentially 'sodium free' as it contains less than 1 mmol sodium (23 mg) per ampoule.

Posology and method of administration

Midazolam is a potent sedative agent 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 and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in the table below.

Additional details are provided in the text following the table.

Indication	**Adults < 60 y**	**Adults ≥ 60 y / debilitated or chronically ill**	**Children**

Conscious sedation	**i.v.** Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	**i.v.** Initial dose: 0.5-1 mg Titration doses: 0.5-1 mg Total dose: < 3.5 mg	**i.v. 6 months-5 years** Initial dose: 0.05-0.1 mg/kg Total dose: < 6 mg **i.v. 6-12 years** Initial dose: 0.025-0.05 mg/kg Total dose: < 10 mg **rectal > 6 months** 0.3-0.5 mg/kg **i.m. 1-15 years** 0.05-0.15mg/kg
Anaesthesia premedication	**i.v.** 1-2 mg repeated **i.m.** 0.07-0.1 mg/kg	**i.v.** Initial dose: 0.5 mg Slow uptitration as needed **i.m.** 0.025-0.05 mg/kg	**rectal > 6 months** 0.3-0.5 mg/kg **i.m. 1-15 years** 0.08-0.2 mg/kg
Anaesthesia induction	**i.v.** 0.15-0.2 mg/kg (0.3-0.35 without premedication)	**i.v.** 0.05-0.15 mg/kg (0.15-0.3 without premedication)	
Sedative component in combined anaesthesia	**i.v.** intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	**i.v.** lower doses than recommended for adults < 60 years	
Sedation in ICU	**i.v.** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		**i.v. in neonates ≤ 32 weeks gestational age** 0.03 mg/kg/h **i.v. in neonates > 32 weeks and children up to 6 months** 0.06 mg/kg/h **i.v. > 6 months** Loading dose: 0.05-0.2 mg/kg Maintenance dose: 0.06-0.12 mg/kg/h

CONSCIOUS SEDATION DOSAGE

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The dose must be individualised and titrated, and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

***Adults*:** the i.v. injection of midazolam should be given slowly at a rate of approximately 1 mg in 30 seconds.

Adults below the age of 60: the initial dose is 2 to 2.5 mg given 5 to 10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.

Adults over 60 years of age, debilitated or chronically ill patients**:** the initial dose must be reduced to 0.5 to 1.0 mg and given 5 to 10 minutes before the beginning of the procedure. Further doses of 0.5 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

Children i.v. administration: midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. One must wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.

Children less than 6 months of age: paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.

Children 6 months to 5 years of age: initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

Children 6 to 12 years of age: initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

Children 12 to 16 years of age: should be dosed as adults.

Children rectal administration**:** the total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml. Total dose should be administered at once and repeated rectal administration avoided.

The use in children less than 6 months of age is not recommended, as available data in this population are limited.

Children i.m. administration**:** the doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0 mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection is painful.

In children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

ANAESTHESIA DOSAGE-PREMEDICATION

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.v. or i.m., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below). Close and continuous monitoring of the patients after administration of premedication is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

Adults: For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 1 to 2 mg i.v. repeated as needed, or 0.07 to 0.1 mg/kg administered i.m. The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated or chronically ill patients. The recommended initial i.v. dose is 0.5 mg and should be slowly up titrated as needed. A dose of 0.025 to 0.05 mg/kg administered i.m. is recommended. In case of concomitant administration of narcotics the midazolam dose should be reduced**.** The usual dose is 2 to 3 mg.

Neonates and children up to 6 months of age: The use in children less than 6 months of age is not recommended as available data are limited.

Children over 6 months of age, rectal administration: The total dose of midazolam, usually ranging from 0.3 to 0.5 mg/kg should be administered 15 to 30 minutes before induction of anaesthesia. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Children over 6 months of age, i.m. administration**:** As i.m. injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2 mg/kg of midazolam administered i.m. has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.

In children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

ANAESTHESIA DOSAGE-INDUCTION

Adults: If midazolam is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced, at times to as low as 25 % of the usual initial dose of the individual agents. The desired level of anaesthesia is reached by stepwise titration. The i.v. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

Premedicated adults below the age of 60 years: an i.v. dose of 0.15 to 0.2 mg/kg will usually suffice.

Non-premedicated adults below the age of 60: the dose may be higher (0.3 to 0.35 mg/kg i.v.). If needed to complete induction, increments of approximately 25 % of the patient's initial dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

Premedicated adults over 60 years of age, debilitated or chronically ill patients: the dose should significantly be reduced e.g. down to 0.05 to 0.15 mg/kg administered i.v. over 20 to 30 seconds and allowing 2 minutes for effect.

Non-premedicated adults over 60 years of age: usually require more midazolam for induction; an initial dose of 0.15 to 0.3 mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.15 to 0.25 mg/kg will usually suffice.

SEDATIVE COMPONENT IN COMBINED ANAESTHESIA

Adults: Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. midazolam (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.

Adults over 60 years of age, debilitated or chronically ill patients: lower maintenance doses will be required.

SEDATION IN INTENSIVE CARE UNITS
The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus, 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.

Neonates and children up to 6 months of age: Midazolam should be given as a continuous i.v. infusion, starting at 0.03 mg/kg/h (0.5 μg/kg/min) in neonates with a gestational age ≤ 32 weeks, or 0.06 mg/kg/h (1 μg/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months. Intravenous loading doses is not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. Careful monitoring of respiratory rate and oxygen saturation is required.

Children over 6 months of age: In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 μg/kg/min). The rate of infusion can be increased or decreased (generally by 25 % of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of midazolam can be administered to increase or maintain the desired effect.

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.

In premature infants, neonates and children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

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 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

Admixture with Hartmann's solution is not recommended as the potency of midazolam decreases.

Shelf life

5 years.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions (for dilution, see also section 'Special precautions for disposal and other handling').

Special precautions for storage

Keep Hypnovel ampoules in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product see section 'shelf life'.

Special precautions for disposal and other handling

Hypnovel solution is stable, both physically and chemically, for up to 24 hours at 2 to 8 °C when mixed aseptically with 500 ml infusion fluids containing any of the following:

- Dextrose 4 % with Sodium Chloride 0.18 %
- Dextrose 5 %
- Sodium Chloride 0.9 %.

Hypnovel ampoules are for single use only. Discard any unused solution.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

There is no evidence of the adsorption of midazolam onto the plastic of infusion apparatus or syringes.

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

This healthcare professional leaflet was last revised in January 2020