

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hypnomidate™ 2 mg/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Hypnomidate contains etomidate 2 mg.

Excipient with known effect

This medicine contains 362.6 mg propylene glycol in 1ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypnomidate is an intravenous induction agent of anaesthesia.

4.2 Posology and method of administration

For intravenous administration.

Hypnomidate should be injected slowly by the intravenous route.

The product must only be used by physicians trained in endotracheal intubation. Equipment for artificial respiration must be available.

It is recommended to wear gloves while opening the ampoule. In the case of any accidental dermal exposure, rinse the affected area with water. Avoid use of soap, alcohol and other cleaning materials that may cause chemical or physical abrasions to the skin.

Adults and children:

A dose of 0.3 mg/kg bodyweight given intravenously at induction of anaesthesia, gives sleep lasting from 4 to 5 minutes.

Dosage should be adjusted to the individual patient response and to clinical effects.

In children under 15 years of age the dosage may need to be increased: a supplementary dose of up to 30% of the normal dose for adults is sometimes necessary to obtain the same depth and duration of sleep as obtained in adults.

Elderly:

A dose of 0.15-0.2 mg/kg bodyweight should be given and the dose should be further adjusted according to the individual patient response and to clinical effects (see Section 4.4 Special Warnings and Precautions for Use).

Since Hypnomidate has no analgesic action, appropriate analgesics should be used in procedures involving painful stimuli.

Hypnosis can be prolonged by additional injections of Hypnomidate.

Do not exceed a total dose of 30 ml (3 ampoules) per procedure.

Hypnomidate may be diluted with sodium chloride infusion BP or dextrose infusion BP but it is not compatible with compound sodium lactate infusion BP (Hartmann's solution). Combinations with pancuronium bromide may show a very slight opalescence; for this reason the two should not be mixed together.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings: In patients with liver cirrhosis, or in those who have already received neuroleptic, opiate or sedative agents, the dose of etomidate should be reduced.

Induction with Hypnomidate may be accompanied by a slight and transient drop in blood pressure due to a reduction of the peripheral vascular resistance. In debilitated patients in whom hypotension may be harmful, the following measures should be taken:

1. Keep the patient supine during induction.
2. Ensure good intravenous access to manage circulatory blood volume.
3. Give Hypnomidate by slow intravenous injection (e.g. 10 ml in 1 min.).
4. Avoid giving other induction agents if possible.

When Hypnomidate is used, resuscitation equipment should be readily available to manage respiratory depression and the possibility of apnoea.

Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels (See section 5.1 Pharmacodynamic Properties).

Where concern exists for the patients undergoing severe stress, particularly those with adrenocortical dysfunction, supplementation with exogenous cortisol should be considered.

Etomidate should be used with caution in critically ill patients, including patients with sepsis.

Prolonged suppression of endogenous cortisol and aldosterone may occur as a direct consequence of etomidate when given by continuous infusion or in repeated doses. Use of Hypnomidate for maintenance of anaesthesia should therefore be avoided. In such situations stimulation of the adrenal gland with adrenocorticotrophic hormone (ACTH) is not useful. However, when etomidate is used for induction, the post-operative rise in serum cortisol which has been observed after thiopentone induction is delayed for approximately 3-6 hours.

Spontaneous movements may occur in one or more groups of muscles, particularly when no premedication has been administered. These movements have been ascribed to subcortical disinhibition. They can be largely prevented by the intravenous administration of small doses of fentanyl, with diazepam 1-2 min. before induction with Hypnomidate.

Myoclonus and pain on injection, including venous pain, is observed during the administration of Hypnomidate especially when it is injected into a small vein. This can largely be avoided by intravenous application of a small dose of suitable opioids, e.g. fentanyl, 1 to 2 minutes before induction.

Hypnomidate should be used with caution in elderly patients, since the potential exists for decreases in cardiac output, which have been reported with doses greater than recommended (see Section 4.2 Posology and Method of Administration for recommended dose in the elderly).

Convulsions may occur in unpremedicated patients.

Precautions: Hypnomidate by injection should be given slowly (e.g. 10 ml over 30-60 seconds).

This medicine contains 3626 mg propylene glycol in 10 ml.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction

The hypnotic effect of etomidate may be enhanced by neuroleptic drugs, opioids, sedatives and alcohol.

Induction with etomidate may be accompanied by a slight and transient reduction in peripheral resistance which may enhance the effect of other drugs reducing blood pressure.

Hypnomidate is pharmacologically compatible with the muscle relaxants, premedicant drugs and inhalation anaesthetics in current clinical use.

Effect of Other Drugs on Etomidate

Co-administration of etomidate with alfentanil has been reported to decrease the terminal half-life of etomidate to approximately 29 minutes. Caution should be used when both drugs are administered together as the concentrations of etomidate may drop below the hypnotic threshold.

The total plasma clearance and volume of distribution of etomidate is decreased by a factor of 2 to 3 without a change in half-life when administered with fentanyl IV. When etomidate is co-administered with fentanyl IV, the dose may need to be reduced.

Effect of Etomidate on Other Drugs

Co-administration of etomidate and ketamine appears to have no significant effect on the plasma concentrations or pharmacokinetic parameters of ketamine or its principal metabolite, norketamine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). Safety in human pregnancy has not been established. Hypnomidate should be used during pregnancy only if the potential benefit justifies the risks to the fetus.

During obstetric anaesthesia etomidate crosses the placenta. The Apgar scores of neonates whose mothers have received Hypnomidate are comparable to those of neonates born after the use of other hypnotic agents. A transient fall in cortisol levels lasting about 6 hours was observed in the neonate after the mother was given Hypnomidate. The decreased values remained within the normal range.

Breast-feeding

Etomidate has been identified in breast milk. The effect of etomidate on neonates is unknown. Breast-feeding should be discontinued during treatment and for a period of approximately 24 hours after treatment with Hypnomidate.

Fertility

In a reproduction study in animals, results showed that Hypnomidate has no effect on fertility at recommended doses.

4.7 Effects on ability to drive and use machines

Etomidate has a major influence on the ability to drive and use machines. Even though a patient may regain normal alertness 30 to 60 minutes after awakening, it is

recommended that patients do not drive or use machines for at least 24 hours after administration of Hypnomidate. Hence, a decision to allow for driving or operating machinery must be a judgment made by the post-anaesthesiology treatment team.

4.8 Undesirable effects

The safety of Hypnomidate was evaluated in 812 subjects who participated in 4 open-label clinical trials of Hypnomidate used for the induction of general anaesthesia.

These subjects took at least one dose of Hypnomidate and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported ($\geq 5\%$ incidence) adverse drug reactions (ADRs) were (with % incidence) dyskinesia (10.3) and vein pain (7.6).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of Hypnomidate from either clinical trial or postmarketing experiences.

The displayed frequency categories use the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available clinical trial data).

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Not Known
Immune System Disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, anaphylactoid reaction)
Endocrine Disorders	Cortisol decreased			Adrenal insufficiency
Nervous System Disorders	Dyskinesia	Myoclonus	Hypertonia, Muscle contractions involuntary, Nystagmus	Convulsion (including grand mal convulsion)
Cardiac Disorders			Bradycardia, Extrasystoles, Ventricular extrasystoles	Cardiac arrest, Atrioventricular block complete

Vascular Disorders		Vein pain, Hypotension	Phlebitis, Hypertension	Shock, Thrombophlebitis (including superficial thrombophlebitis and deep vein thrombosis)
Respiratory, Thoracic and Mediastinal Disorders		Apnoea, Hyperventilation, Stridor	Hypoventilation, Hiccups, Cough	Respiratory depression, Bronchospasm (including fatal outcome)

Gastrointestinal Disorders		Vomiting, Nausea	Salivary hypersecretion	
Skin and Subcutaneous Tissue Disorders		Rash	Erythema	Stevens-Johnson syndrome, Urticaria
Musculoskeletal and Connective Tissue Disorders			Muscle rigidity	Trismus
General Disorders and Administration Site Conditions			Injection site pain	
Injury, Poisoning and Procedural Complications			Anaesthetic complication, Delayed recovery from anaesthesia, Inadequate analgesia, Procedural nausea	

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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdosing is likely to result in prolonged anaesthesia with the possibility of respiratory depression and even arrest, in which case adequate respiratory support is mandatory. Hypotension has also been observed. Overdosage may depress cortical secretion. This may be associated with disorientation and delayed awakening.

Treatment

General supportive measures and close observation are recommended. In addition, administration of 50 - 100 mg hydrocortisone (not ACTH) may be required for depression of cortisol secretion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anesthetics, ATC code N01AX07
Etomidate is a short acting intravenous hypnotic which is rapidly inactivated by enzyme metabolism so that it does not give rise to a hangover effect. It does not release histamine, and has no effect on liver function. *In vitro* studies have shown etomidate to be an inhibitor of microsomal enzymes. Limited *in vivo* studies have demonstrated only minimal inhibition of hepatic metabolism.

Adrenal Suppression

Etomidate when used for the introduction of anaesthesia, produces a decrease in plasma cortisol and aldosterone, which remains suppressed for 6-8 hours. These levels usually return to baseline within 24 hours. Etomidate appears to be a specific and reversible inhibitor of the 11-beta-hydroxylation of adrenal steroid synthesis.

5.2 Pharmacokinetic properties

Profile in Plasma:

After intravenous administration, the time-course of the etomidate plasma levels can be described by a three-compartment model reflecting distribution, metabolism, and elimination processes. Plasma concentrations decrease rapidly for about 30 minutes and then more slowly; traces are still detectable after about 6 hours. Metabolites, chiefly of hydrolysis, are more slowly excreted.

Distribution

Etomidate is approximately 76.5% bound to plasma proteins. Etomidate is rapidly distributed to the brain and other tissues. Its volume of distribution is about 4.5 L/kg.

Metabolism and Elimination

Etomidate is metabolized in the liver. After 24 hours, 75% of the administered dose of etomidate has been eliminated in the urine primarily as metabolites. Only 2% of etomidate is excreted unchanged via the urine. The terminal half-life of about 3 to 5 hours reflects the slow distribution of etomidate from the deep peripheral compartment.

5.3 Preclinical safety data

In a reproductive fertility study, results showed no effects on fertility or general pregnancy parameters. In standard embryotoxicity and teratology studies, some mortality occurred in the high dose groups (5 mg/kg). Administration of etomidate during the peri- and post-natal period, resulted in some dose-related maternal mortality and toxicity, and attributed to this, some slight decrease in pup survival in the high dose group (5 mg/kg). No adverse effects were observed

on pregnancy rate, litter size, birthweight, or body weight gain.

Published studies in animals (including primates) at doses resulting in light to moderate anesthesia demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Water for injections
1N sodium hydroxide*
1N hydrochloric acid*

* for occasional pH adjustment only

6.2 Incompatibilities

Combinations with pancuronium bromide may show a very slight opalescence; for this reason the two should not be mixed together.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Colourless glass ampoule, Ph.Eur Type I, containing 10 ml Hypnomidate, in packs of 5 and 10 ampoules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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AUTHORISATION**

08/07/2009

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25/03/2024