ETOMIDATE (HYPNOMIDATE®)
CORE SAFETY PROFILE
July 2012 (DE/H/PSUR/0025/001)

4.2 Posology and method of administration

HYPNOMIDATE ampoules contain a 10-ml ready-for-use solution with 20 mg etomidate, i.e. 2 mg etomidate per ml solution. The effective hypnotic dose of HYPNOMIDATE is 0.3 mg/kg body weight. Therefore, in an adult patient one ampoule usually suffices for a sleep duration of 4-5 min. This dose can be adapted to the body weight.

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

HYPNOMIDATE should be injected slowly by the intravenous route.

Hypnosis can be prolonged by additional injections of HYPNOMIDATE.

Do not exceed the total amount of 3 ampoules (30 ml).

Since HYPNOMIDATE has no analgesic effect, it is recommended to administer a suitable opioid, e.g. 1-2 ml fentanyl intravenously 1-2 min. before the HYPNOMIDATE injection.

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

In the elderly, a single dose of 0.15 - 0.2 mg/kg body weight should be given and the dose should be further adjusted according to effects (see Section 4.4 Special Warnings and Special Precautions for Use and Section 5.2 Special Populations: Elderly).

In children under 15 years 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 (see Section 5.2 Special Populations: Children).
4.3 Contraindications

HYPNOMIDATE is contraindicated in patients with a known hypersensitivity to the drug or its components.

4.4 Special warnings and precautions for use

A HYPNOMIDATE injection should only be administered intravenously.

Anaesthesia with HYPNOMIDATE can be carried out without additional risks in patients with epilepsy, glaucoma or porphyria or with a known history of malignant hyperthermia.

Induction with HYPNOMIDATE may be accompanied by a slight and transient drop in blood pressure due to a reduction of the peripheral vascular resistance (especially after previous administration of droperidol). In debilitated patients in whom hypotension may be hazardous, the following measures should be taken:

1. Before induction, intravenous access should be obtained for the management of circulatory blood volume.
2. Other inducing agents should be avoided to the extent possible.
3. The induction should be carried out with the patient supine.
4. The drug should be injected slowly (e.g. 10 ml in 1 min.).

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

Induction doses of etomidate have been associated with a reduction in plasma cortisol and aldosterone concentrations (See Section 5.1 Pharmacodynamic Properties). These have not been associated with changes in vital signs or evidence of increased mortality; however.

Where concern exists for patients undergoing severe stress, particularly those with adrenocortical dysfunction, supplementation with exogenous cortisol should be considered. In such situations stimulation of the adrenal gland with ACTH is not useful.

Prolonged suppression of endogenous cortisol and aldosterone may occur as a direct consequence of etomidate when given by continuous infusion or in repeated doses and therefore should be avoided.
In such situations stimulation of the adrenal gland with ACTH is not useful.

**Etomidate should be used with caution in patients with underlying cortico-adrenal insufficiency such as patients with sepsis.**

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

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 droperidol or 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).

Since HYPNOMIDATE has no analgesic action, appropriate analgesics should be used during surgical procedures.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Sedative drugs potentiate the hypnotic effect of HYPNOMIDATE.** The hypnotic effect of etomidate may be enhanced by neuroleptic drugs, opioids and sedatives, and by 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.**

**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 Pregnancy and lactation

In animals HYPNOMIDATE has no primary effect on fertility, nor primary embryotoxic nor teratogenic effects. At maternally toxic doses in rats, decreased survival was noted. HYPNOMIDATE should be used during pregnancy only if the potential benefit justifies the risks to the fetus.

During obstetric anaesthesia, etomidate may cross the placenta. The Apgar scores of newborns whose mothers have received etomidate are comparable to those of infants 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.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, however, caution should be exercised when HYPNOMIDATE is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Etomidate has a major influence on the ability to drive and use machines. It is not recommended to use potentially dangerous machinery or to drive a car during the first 24 hours after administration. The return of normal alertness may vary according to the duration of the operation, the total dose of etomidate administered and concomitant medication used. 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 1 dose of HYPNOMIDATE and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported (≥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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
<th>Frequency Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
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<tr>
<td>Immune System Disorders</td>
<td>Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, anaphylactoid reaction)</td>
<td></td>
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<tr>
<td>Endocrine Disorders</td>
<td>Adrenal insufficiency</td>
<td></td>
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<tr>
<td>Nervous System Disorders</td>
<td>Convulsion (including grand mal convulsion)</td>
<td></td>
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<td></td>
<td>Cardiac arrest, Atrioventricular block complete</td>
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<tr>
<td>Cardiac Disorders</td>
<td>Bradycardia, Extrasystoles, Ventricular extrasystoles</td>
<td></td>
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<tr>
<td>Vascular Disorders</td>
<td>Phlebitis, Hypertension</td>
<td></td>
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<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Shock, Thrombophlebitis (including superficial thrombophlebitis and deep vein thrombosis)</td>
<td></td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>Respiratory depression, Bronchospasm (including fatal outcome)</td>
<td></td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Stevens-Johnson syndrome, Urticaria</td>
<td></td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Trismus</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Injection site pain</td>
<td></td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Anaesthetic complication, Delayed recovery from anaesthesia, Inadequate analgesia, Procedural nausea</td>
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### 4.9 Overdose

**Symptoms**

An overdose of etomidate, administered as a bolus, deepens sleep and may cause respiratory depression and even respiratory arrest, in which case adequate respiratory support is mandatory. Hypotension has also been observed in such cases. Overdosage may depress cortical secretion. This may be associated with disorientation and delayed awakening.
Treatment

In addition to supportive measures (e.g. of respiration) administration of 50-100 mg hydrocortisone (not ACTH) may be required.