PROPOSED PACKAGE INSERT –May 2010

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SCHEDULING STATUS
Schedule 5.

PROPRIETARY NAME (and dosage form)
HYPNOMIDATE® Injection.

COMPOSITION
HYPNOMIDATE is supplied as an injectable solution in 10 ml ampoules.
Each 10 ml ampoule contains 20 mg Etomidate (2 mg/ml) in propylene glycol and water.

PHARMACOLOGICAL CLASSIFICATION
A.2.2 Central nervous system depressants. Sedatives, hypnotics.

PHARMACOLOGICAL ACTION
Pharmacodynamics:
Etomidate is a short-acting intravenous anaesthetic agent unrelated to existing intravenous induction agents. It has no analgesic properties and therefore appropriate analgesic agents should be used concomitantly. In adults 0.3 mg/kg bodyweight induces hypnosis within 10 seconds, which lasts about 5 minutes (or generally longer in patients premedicated with sedatives).

Adrenal Suppression
Etomidate, when used for the induction of anaesthesia, produces a decrease in plasma cortisol and aldosterone, which remains suppressed for 6 to 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.
Pharmacokinetics:

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.

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 rapidly hydrolysed, predominantly 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.

Concentration-Effect Relationship

The minimal plasma concentration inducing a hypnotic effect is about 0.3 µg/ml.

Special Populations:

Children: In a study conducted in 12 children (age 7-13 years, weight 22-48 kg), weight-adjusted initial volume of distribution was 2.4-fold higher than in adults (0.66 vs. 0.27 L/kg) and drug clearance in children was approximately 58% higher than in adults. These data suggest the need for higher doses in children compared to adults.

Hepatic Impairment: The elimination half-life has been reported to be prolonged in cirrhotic patients who have received etomidate in combination with fentanyl. A reduction in the infusion rate should be considered in these patients.

Elderly: Etomidate clearance is decreased in elderly subjects (>65 years of age) compared to younger subjects. Early plasma concentrations are higher in elderly subjects due to a
smaller initial volume of distribution in these subjects compared to younger subjects. Dosage requirements may therefore be reduced in elderly subjects.

INDICATIONS
HYPNOMIDATE is indicated for the induction of general anaesthesia. It may be used as an anaesthetic for short painless procedures such as cardio version, uterine curettage etc. Because HYPNOMIDATE has no analgesic effect it is not suitable as a mono-anaesthetic.

CONTRA-INDICATIONS
HYPNOMIDATE is contra-indicated in patients with known hypersensitivity to etomidate or its components.

HYPNOMIDATE suppresses adrenocortical function and should not be used in patients with adrenocortical function that is already reduced or at risk of being reduced.

HYPNOMIDATE infusions suppress adrenocortical function and sudden death may occur.

INTERACTIONS
Sedative medicines potentiate the hypnotic effect of HYPNOMIDATE.

Co-administration of HYPNOMIDATE with alfentanil has been reported to decrease the terminal half-life of etomidate to approximately 29 minutes. Caution should be used when both medicines are administered together as the concentrations of HYPNOMIDATE 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 HYPNOMIDATE is co-administered with fentanyl IV, the dose may need to be reduced
Co-administration of HYPNOMIDATE and ketamine appears to have no significant effect on the plasma concentrations or pharmacokinetic parameters of ketamine or its principal metabolite, norketamine.

**PREGNANCY AND LACTATION**

The safety of HYPNOMIDATE in human pregnancy has not been established.

During obstetric anaesthesia, etomidate may cross the placenta. A 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.

Safety in lactation has not been established.

**DOSAGE AND DIRECTIONS FOR USE**

HYPNOMIDATE ampoules contain a 10-ml ready-for-use solution with 20 mg etomidate, i.e. 2 mg etomidate per ml solution.

HYPNOMIDATE is effective in doses ranging between 0,2 and 0,3 mg/kg (0,1 and 0,15 ml per kg) body weight. Therefore, in an adult patient one ampoule usually suffices for a sleep duration of about 5 minutes. This dose can be adapted to the body weight.

HYPNOMIDATE should be administered intravenously within 60 seconds.

Hypnosis can be prolonged by additional injections of HYPNOMIDATE.

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

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 “Special Precautions” and Pharmacokinetics – Special Populations: Elderly").
In children under 15 years the dosage should 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 “Pharmacokinetics – Special Populations: Children”)

**Instructions for Use and Handling**

**Ampoules:**

1. Maintain the ampoule between thumb and index, leaving the tip of the ampoule free.

2. With the other hand, hold the tip of ampoule putting the index against the neck of ampoule, and the thumb on the coloured point in parallel to the identification coloured ring(s).

3. Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**

**Clinical Trial data:**
ADRs listed below by system organ class and frequency. Frequencies are defined as: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Nervous system disorder

Very common: Dyskinesia

Common: Myclonus

Uncommon: Hypertonia, Muscle contractions involuntary, Nystagmus

Vascular disorders

Common: Vein pain, Hypotension

Uncommon: Hypertension, Phlebitis

Cardiac disorders

Uncommon: Bradycardia, Extrasystoles, Ventricular extrasystoles

Respiratory, Thoracic and mediastinal disorders

Common: Apnoea, Hyperventilation, Stridor

Uncommon: Cough, Hiccups, Hypoventilation

Gastrointestinal disorders

Common: Vomiting, Nausea

Uncommon: Salivary secretion

Skin and Subcutaneous Tissue disorder

Common: Rash

Uncommon: Erythema

Musculoskeletal and connective tissue disorders

Uncommon: Muscle rigidity

General disorders and Administration site Conditions

Uncommon: Injection site pain

Injury, Poisoning and Procedural complications

Uncommon: Anaesthetic complication, Delayed recovery from anaesthesia, Inadequate analgesia

Procedural nausea

Postmarketing data
Adverse drug reactions first identified during postmarketing experience with HYPNOMIDATE and based on spontaneous reporting are:

**Immune System Disorder**

Hypersensitivity (such as anaphylactic shock, anaphylactic reaction and anaphylactoid reaction)

**Endocrine Disorder**

Adrenal insufficiency

**Nervous system Disorder**

Convulsion (including grand mal convulsion)

**Cardiac Disorder**

Cardiac arrest, atrioventricular block complete

**Vascular Disorders**

Shock, thrombophlebitis (including superficial thrombophlebitis and deep vein thrombosis)

**Respiratory, Thoracic and mediastinal Disorders**

Respiratory depression, bronchospasm (including fatal outcome)

**Skin and Subcutaneous Tissue disorder**

Stevens-Johnson syndrome, urticaria

**Musculoskeletal and connective tissue Disorders**

Trismus

**Special Precautions:**

HYPNOMIDATE should only be administered intravenously.

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 medicine should be injected slowly (e.g. 10 ml in 1 minute).

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 “Pharmacodynamics”). 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 HYPNOMIDATE when given by continuous infusion or in repeated doses and therefore should be avoided.

In patients with liver cirrhosis, or in those who have already received neuroleptic, opiate or sedative agents, the dose of HYPNOMIDATE 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 “Dosage and Directions for Use” for recommended dose in the elderly).

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

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

**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 by prolonged infusion may severely depress cortical secretion. This may be associated with disorientation and delayed awakening.

**Treatment:**
Supportive and symptomatic.

**IDENTIFICATION**
A clear, colourless solution in a 10-ml glass ampoule.

**PRESENTATION**
10-ml colourless glass ampoules containing 2 mg/ml HYPNOMIDATE in a ready to use solution, packed in boxes of 5 ampoules.

**STORAGE INSTRUCTIONS**
Store below 25°C.
KEEP OUT OF REACH OF CHILDREN.
REGISTRATION NUMBER

M/2.2/183

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

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