Professional Information for B. Braun Etomidate 2 mg/ml

SCHEDULING STATUS

S5

1. NAME OF MEDICINE

B. BRAUN ETOMIDATE 2 mg/ml (Emlusion for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This emulsion for injection (1 ampoule) contains etomidate 20 mg/10 mL.

Each mL of emulsion for injection contains etomidate 2 mg.

Excipients with known effect:

Each 10 mL ampoule of emulsion contains:

Soya-bean oil, refined	1,0 g
Sodium oleate	3,0 mg (see section 4.4)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection.

Milky-white oil-in-water emulsion.

pH 6,0 – 8,5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

B. BRAUN ETOMIDATE 2 mg/ml is indicated for the induction of general anaesthesia. Etomidate is also indicated as an anaesthetic for short painless procedures such as cardio version, uterine curattage etc.

Because B. BRAUN ETOMIDATE 2 mg/ml has no analgesic effect and it is not suitable as a mono-anaesthetic.

4.2 Posology and method of administration

Posology

B. BRAUN ETOMIDATE 2 mg/ml ampoules contain a ready-for-use emulsion containing 2 mg etomidate per mL of emulsion.

Adults

B. BRAUN ETOMIDATE 2 mg/ml doses range between 0,2 and 0,3 mg/kg (0,1 and 0,15 mL per kg) body mass. Therefore, in an adult patient one ampoule usually suffices for a sleep duration of about 5 minutes.

This medicine should be administered intravenously over 60 seconds. Hypnosis can be prolonged by additional injections of B. Braun Etomidate 2 mg/mL.

Do not exceed the total amount of three ampoules (30 mL).

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

Paediatric population

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 section 5.2)

Elderly

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 and section 5.2)

Other special patient groups

In patients with liver cirrhosis or those who have already received neuroleptic, opiate or sedative medication, the dose of etomidate should be reduced (see section 4.5 and section 5.2).

Method of administration

B. BRAUN ETOMIDATE 2 mg/ml is for intravenous administration only.

4.3 Contraindications

B. BRAUN ETOMIDATE 2 mg/ml should not be used in patients with adrenocortical function that is already reduced, as etomidate suppresses adrenocortical function. B. BRAUN ETOMIDATE 2 mg/ml infusions suppress adrenocortical function and sudden death may occur.

B. BRAUN ETOMIDATE 2 mg/ml is contraindicated

- In patients with known hypersensitivity to etomidate, soya, peanut or to any of the excipients listed in section 6.1 (see also section 4.8)
- In patients with Porphyria
- Pregnancy and lactation (see section 4.6)
- Labour and delivery (see section 4.6)
- Neonates and infants up to the age of 6 months should be excluded from treatment with B. BRAUN ETOMIDATE 2 mg/ml except for imperative indications during in-patient treatment.

4.4 Special warnings and precautions for use

Special warnings

Induction with B. BRAUN ETOMIDATE 2 mg/ml may cause a slight and transient drop in blood pressure due to a decrease in peripheral vascular resistance (especially

when fentanyl and/or droperidol are used as premedication). In debilitated patients in whom hypotension may be unsafe, the following measures should be taken:

1. Set up an infusion before the induction of anaesthesia, to facilitate subsequent volume replacement.
2. Restrict the use of other compounds which may cause hypotension (see section 4.5).
3. Perform the induction with the patient in a recumbent position.
4. Inject the medicine slowly (over 1 minute).
5. Spontaneous movements of one or more muscle groups (myoclonus) may occur, especially when no premedication has been administered. These movements are attributed to a disinhibition of subcortical centres and can largely be prevented by intravenous administration of small doses of fentanyl, or diazepam, 1 – 2 minutes before induction with B. BRAUN ETOMIDATE 2 mg/ml.

Etomidate inhibits the adrenocortical biosynthesis of steroids. Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol and aldosterone levels, unresponsive to ACTH administration. When etomidate is used for induction, the postoperative rise of serum cortisol observed after thiopentone in-duction is delayed for approximately 3 – 6 hours (see section 5.1).

Where concern exists for patients undergoing severe stress, particularly those with adrenocortical dysfunction, supplementation with exogenous cortisol (e.g. 50 – 100 mg hydrocortisone) 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.

Use of etomidate for maintenance of anaesthesia should therefore be avoided. In such situations stimulation of the adrenal gland with ACTH is not useful.

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

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

Myoclonus and local pain on injection, which is usually mild, is observed during the administration of B. BRAUN ETOMIDATE 2 mg/ml especially when it is injected undiluted 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. To minimise the risk of local pain, larger veins should be used.

B. BRAUN ETOMIDATE 2 mg/ml 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 sections 4.2 and 5.2).

In animal experiments, B. BRAUN ETOMIDATE 2 mg/ml has been shown to possess a porphyrogenic potential. Therefore it should not be administered to patients with hereditary disorder of haem biosynthesis, unless there is no safer alternative.

Precautions for use

Since B. BRAUN ETOMIDATE 2 mg/ml has no analgesic action, appropriate analgesics should be used during surgical procedures. If used for short-term

narcosis, a strong analgesic, e. g. fentanyl, must be given prior to or simultaneously with B. BRAUN ETOMIDATE 2 mg/ml (see sections 4.2 and 5.2). Attention should be paid also to instructions given in sections 4.5 and 6.6.

B. BRAUN ETOMIDATE 2 mg/ml may be used only by a doctor skilled in endotracheal intubation.

When B. BRAUN ETOMIDATE 2 mg/ml is used, resuscitation equipment should be readily available to manage respiratory depression and the possibility of apnoea.

B. BRAUN ETOMIDATE 2 mg/ml contains less than 1 mmoL (23 mg) sodium (as sodium oleate) per ampoule, i.e. it is essentially sodium-free.

The interference with daily activities may continue for up to 24 hours and no legal/contractual devisions should be entered for 24 hours after receiving anaesthetic/conscious sedation. Alcohol use should also be avoided for the same period.

4.5 Interaction with other medicines and other forms of interaction

The hypnotic effect of etomidate may be enhanced by:

- neuroleptic medicines
- opioids
- sedatives
- alcohol.

The use of alcohol or other CNS depressants should be avoided for 24 hours following B. BRAUN ETOMIDATE 2 mg/ml.

A reduced dose of B. BRAUN ETOMIDATE 2 mg/ml may be necessary in patients who have received antipsychotics, sedatives or opioids.

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

Alfentanil

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 medicines are administered together as the concentrations of etomidate may drop below the hypnotic threshold.

Fentanyl

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 intravenously. When etomidate is co-administered with fentanyl intravenously, the dose may need to be reduced.

Ketamine

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.

Adrenergic neurone blockers, alpha blockers

Combination with general anaesthetics leads to an enhancement of the hypotensive effect of these medicines.

Calcium channel blockers (Verapamil, Diltiazem)

Combination with general anaesthetics results in an enhancement of the hypotensive effect and also AV delay.

Monoamine oxidase inhibitors (MAOI)

Because of hazardous interactions between general anaesthetics and MAOIs, MAOIs should normally be stopped 2 weeks before surgery.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of the use of B. BRAUN ETOMIDATE 2 mg/ml during pregnancy has not yet been established. Studies in animals have shown reproductive toxicity. At maternally toxic doses in rats, decreased survival was noted.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic medicines 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.

During obstetric anaesthesia, etomidate may cross the placenta.

A transient fall in cortisol levels lasting about 6 hours was observed in the neonate after the mother was given etomidate. The decreased values remained within the normal range.

Breast-feeding

Etomidate is excreted into human milk. Caution should be exercised when B. BRAUN ETOMIDATE 2 mg/ml is administered to a nursing mother.

If B. BRAUN ETOMIDATE 2 mg/ml must be given during the lactation period, nursing is to be interrupted and not to be resumed 24 hours after administration; breast milk secreted during this period must be discarded.

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 machines 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

a. Summary of the safety profile

Like most general anaesthetics, etomidate may affect respiratory and vascular functions. Like some other general anaesthetics, etomidate may cause involuntary muscle movements. Besides this, etomidate frequently affects adrenocortical functions.

b. Tabulated list of adverse reactions

System Organ Class	Frequency Classification	Undesirable Effects
Immune System Disorders	Frequency unknown	Hypersensitivity[1] (such as anaphylactic shock, anaphylactic reaction, anaphylactoid reaction)
Endocrine Disorders	Frequent	Cortisol decreased
	Frequency unknown	Adrenal insufficiency
Nervous System Disorders	Frequent	Dyskinesia Myoclonus
	Less Frequent	Hypertonia, Muscle contractions involuntary, Nystagmus, Shivering
	Frequency unknown	Convulsion (including grand mal convulsion)
Cardiac Disorders	Less Frequent	Bradycardia,

		Extrasystoles, Ventricular extrasystoles
	Frequency unknown	Cardiac arrest, Atrioventricular block complete
Vascular Disorders	Frequent	Hypotension
	Less Frequent	Hypertension, Phlebits
	Frequency unknown	Shock
Respiratory, Thoracic and Mediastinal Disorders	Frequent	Apnoea[2], Hyperventilation, Stridor
	Less Frequent	Hypoventilation, Hiccups, Cough Laryngospasm
	Frequency unknown	Respiratory depression[2], Bronchospasm (including fatal outcome)
Gastrointestinal Disorders	Frequent	Vomiting, Nausea
	Less Frequent	Salivary hypersecretion
Skin and Subcutaneous Tissue Disorders	Frequent	Rash
	Less Frequent	Erythema
	Frequency unknown	Stevens-Johnson syndrome, Urticaria
Musculoskeletal and Connective Tissue Disorders	Less Frequent	Muscle rigidity
	Frequency unknown	Trismus
General Disorders and Administration Site Conditions	Less Frequent	Injection site pain
Injury, Poisoning and Procedural Complications	Less Frequent	Anaesthetic complication, Delayed recovery from anaesthesia, Inadequate analgesia, Procedural nausea

[1] After administration of etomidate, release of histamine has been noted.

B. BRAUN ETOMIDATE 2 mg/ml contains soya-bean oil, which may very rarely cause severe allergic reactions.

[2] Respiratory depression and apnoea may occur especially after administration of higher doses of etomidate in combination with central depressant medicines. In patients of 55 years of age or older, respiratory depression and apnoea may occur especially after doses exceeding the recommended maximum dose of 0.2 mg of etomidate per kg body weight.

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 to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://primaryreporting.who-umc.org/ZA.

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

Treatment depends on the nature and severity of the symptoms, including, if necessary, respiratory support.

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

All equipment and medication usually required in general anaesthetic procedures should be available. Supportive measures such as establishing and maintaining a patent airway (intubation, if necessary) and administering oxygen with assisted ventilation are essential.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 2.2 Central nervous system depressants. Sedatives, hypnotics

ATC code: N01AX07

Mechanism of action, pharmacodynamic effects

The effect of etomidate starts at short notice and the duration of the hypnotic effect is short as a result of redistribution and metabolic inactivation. A single dose of 0.3 mg/kg body weight leads to loss of consciousness in 30-60 seconds and to narcosis of 3 – 5 minutes duration, followed by sleep.

Other pharmacological effects

Etomidate suppresses the function of the adrenal cortex. Etomidate inhibits adrenal cell cortisol production by reversibly blocking the steroid synthesis enzyme 11-β-hydroxylase. The cortisol suppression is unresponsive to ACTH and lasts up to 8 h after a single 0,3 mg/kg dose of etomidate. The inhibition of cortisol synthesis is reversible and depends on the etomidate concentration in plasma.

Involuntary muscle movements observed after administration of etomidate result from disinhibition of physiological diencephalic excitations, similar to myoclonus during physiological sleep.

Etomidate has been reported to possess anticonvulsive properties and a protective effect on brain cells against hypoxic damage.

5.2 Pharmacokinetic properties

Absorption

Since B. BRAUN ETOMIDATE 2 mg/ml is administered intravenously, its bioavailability is 100 %.

Distribution

Etomidate rapidly separates from the oil particles upon injection. This is reflected by the etomidate plasma concen-tration, which is comparable with that of the aqueous formulation.

The plasma protein binding of etomidate (primarily to albumin) is about 75 %, it is reduced in renal dysfunction or chronic liver damage.

Etomidate is rapidly distributed to the brain and other tissues.

The total volume of distribution is about 4.5 L/kg.

Rapid distribution from the central compartment to a peripheral and a deeper peripheral compartment as well as a high elimination rate cause the plasma concentration to fall rapidly for about 30 minutes after a single administration. Then, the plasma concentration declines more slowly.

Biotransformation and elimination

The primary step of biotransformation is the hydrolysis of the ethyl ester in the liver. A small proportion is also subject to oxidative N-dealkylation. All metabolites discovered are pharmacologically inactive.

The elimination half-life is relatively long (terminal elimination half-life 2 – 5 h) despite a high rate of hepatic ex-traction due to slow redistribution of etomidate from the deeper peripheral compartment.

About 75 % of the administered dose of etomidate appear in the urine within 24 hours, primarily as metabolites. Other routes of excretion play a minor role.

The major metabolite in the urine (about 80 %) is the hydrolysis product of etomidate, namely R-(+)-1-(α-methylbenzyl)-5-imidazolecarboxylic acid. Only 2 % of etomidate are excreted unchanged via the urine.

The half-life of the lipid particles is short.

Accumulation has not been observed.

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 in adults (0.66 vs 0,27 L/kg) and medicine 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 considerd in these patients (see section 4.2)

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 (see section 4.2)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined

Medium-chain triglycerides

Glycerol

Egg phospholipids for injection

Sodium oleate

Water for injections

6.2 Incompatibilities

B. BRAUN ETOMIDATE 2 mg/ml must not be mixed with other medicinal products.

6.3 Shelf life

Unopened

2 years at 25 °C.

After first opening

To be used immediately, see section 6.6.

After reconstitution / dilution

not applicable

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

For single use only.

Discard any unused portion.

Keep the ampoules in the outer carton until required for use.

6.5 Nature and contents of container

B. BRAUN ETOMIDATE 2 mg/ml emulsion for injection is supplied in a 10 mL Type I, clear, colourless glass ampoule. 5 ampoules will be packed in a clear PVC tray and 2 trays each containing 5 ampoules will be packed into an outer cardboard container.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

Ampoules should be shaken prior to use to ensure homogenous distribution. Only to be used if the emulsion is homogenous and milky-white after shaking. If two layers can be seen after shaking the ampoule should not be used.

Not to be used if ampoule shows signs of damage.

B. BRAUN ETOMIDATE 2 mg/ml does not contain antimicrobial preservatives. Immediately after opening of the ampoule, the emulsion has to be drawn up in a syringe under aseptic conditions and injected, because fat emulsions promote microbial growth. Unused portions must be discarded.

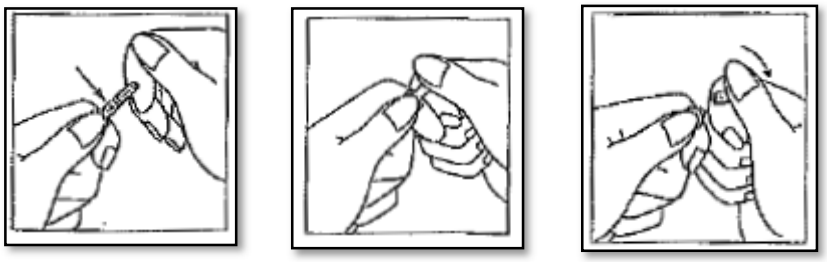
Medicines to be given concurrently with B. BRAUN ETOMIDATE 2 mg/ml, e.g., an analgesic, should be administered consecutively through the same line or through separate venous cannulae.

B. BRAUN ETOMIDATE 2 mg/ml may be injected into the tubing of an infusion of isotonic sodium chloride having temporarily been stopped.

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 indentification 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.



7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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