# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Etomidate 2 mg/ml emulsion for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| | |
|---|---|
| 1 ml of emulsion for injection contains | 2 mg of etomidate |
| 10 ml of emulsion for injection (= 1 ampoule) contain | 20 mg of etomidate |

Excipients with known effect:

One ampoule (10 ml) of emulsion for injection contains:

| | |
|---|---|
| Soya-bean oil, refined | 1.0 g |
| Sodium (as sodium oleate) | 0.23 mg |

For the 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

Etomidate 2 mg/ml is indicated for the induction of general anaesthesia in adults, infants and toddlers older than 6 months, children and adolescents.

### 4.2 Posology and method of administration

Posology

In all patients, the dosage should be adjusted according to the individual response and the clinical effect.

The following dosage guidelines should be followed:

Adults and adolescents

As a rule, the effective hypnotic dose is 0.3 mg of etomidate per kg body weight, corresponding to 0.15 ml of Etomidate 2 mg/ml per kg body weight.

Therefore, in an adult patient one ampoule usually suffices for a sleep duration of 4-5 min.

Hypnosis can be prolonged by additional injections of Etomidate 2 mg/ml.

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

Paediatric population

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.

Elderly patients

Elderly patients should be given a single dose of 0.15 to 0.2 mg of etomidate per kg body weight and the dose should be further adjusted according to effects (see section 4.4).

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.

Method of administration

Intravenous use

Etomidate 2 mg/ml must be injected strictly intravenously and slowly, usually over approximately 30 seconds, in fractions if required.

Intra-arterial injection must be avoided. Paravenous injection causes severe local pain.

The use of narcotic analgesics or diazepam as premedication and during surgery will reduce the uncontrolled spontaneous muscle movements (myoclonus) shown by some patients after Etomidate 2 mg/ml administration (see section 4.4 and 5.1).

Since etomidate has no analgesic effect, it is recommended to administer a suitable opioid, e.g. fentanyl intravenously 1-2 min before the injection of Etomidate 2 mg/ml (see section 4.4 and 5.1).

The product must only be used by physicians trained in endotracheal intubation. Equipment for artificial respiration must be available (see section 4.4).

## 4.3 Contraindications

Hypersensitivity to etomidate, soya, peanut or to any of the excipients listed in section 6.1 (see also section 4.8).

Neonates and infants up to the age of 6 months should be excluded from treatment with Etomidate 2 mg/ml except for imperative indications during in-patient treatment.

## 4.4 Special warnings and precautions for use

*Special warnings*

An injection of Etomidate 2 mg/ml should only be administered intravenously.

Induction with Etomidate 2 mg/ml 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.).

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 induction 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 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 (see also section 4.8). These movements have been ascribed to subcortical disinhibition (see section 5.1). They can be largely prevented by the intravenous administration of small doses of fentanyl, with droperidol or diazepam 1-2 min before induction with Etomidate 2 mg/ml (see also section 4.2).

Myoclonus and local pain on injection, which is usually mild, is observed during the administration of 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.

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 section 4.2).

In animal experiments, 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 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 Etomidate 2 mg/ml (see section 4.2). Attention should be paid also to instructions given in sections 4.5 and 6.6.

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

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

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

## 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
- 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.

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 drugs 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 substances.

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 Etomidate 2 mg/ml during pregnancy has not yet been established. Studies in animals have shown reproductive toxicity (see section 5.3). At maternally toxic doses in rats, decreased survival was noted.

Etomidate 2 mg/ml should be used during pregnancy only if the potential benefit justifies the risks to the foetus.

During obstetric anaesthesia, etomidate may cross the placenta. The Apgar scores of the newborns whose mothers have received etomidate are comparable with 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 etomidate. The decreased values remained within the normal range.

Breast-feeding

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

If 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

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.

Undesirable effects are listed according to their frequencies as follows:

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)
Not known (frequency cannot be estimated from the available data)

| **System Organ Class** | **Adverse Drug Reactions** | | | | |
|---|---|---|---|---|---|
| | **Frequency Category** | | | | |
| | **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) | **Not Known** (cannot be estimated from the available data) |
| **Immune System Disorders** | | | | | Hypersensitivity[1] (such as anaphylactic shock, anaphylactic reaction, anaphylactoid reaction) |
| **Endocrine Disorders** | Cortisol decreased | | | | Adrenal insufficiency |
| **Nervous System Disorders** | Dyskinesia | Myoclonus | Hypertonia, Muscle contractions involuntary, Nystagmus, Shivering | | Convulsion (including grand mal convulsion) |
| **Cardiac Disorders** | | | Bradycardia, Extrasystoles, Ventricular extrasystoles | | Cardiac arrest, Atrioventricular block complete |
| **Vascular Disorders** | | Hypotension | Hypertension | | Shock |
| **Respiratory, Thoracic and Mediastinal Disorders** | | Apnoea[2], Hyperventilation, Stridor | Hypoventilation, Hiccups, Cough | Laryngospasm | Respiratory depression[2], 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 | | |

1) After administration of etomidate, release of histamine has been noted.
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 drugs. 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

## 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.

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics,

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.

Since etomidate has no analgesic effect, concurrent administration of an analgesic is required for all surgical procedures.

## 5.2 Pharmacokinetic properties

Absorption

Since 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 concentration, 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 extraction 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.

## 5.3 Preclinical safety data

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

Soya-bean oil, refined,
Medium-chain triglycerides,
Glycerol,
Egg phospholipids for injection,
Sodium oleate,
Water for injections

## 6.2 Incompatibilities

Etomidate 2 mg/ml must not be mixed with other medicinal products.

## 6.3 Shelf life

Unopened
2 years

After first opening
To be used immediately, see section 6.6.

After reconstitution / dilution
not applicable

## 6.4 Special precautions for storage

Do not freeze.
Keep ampoules in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

The product is supplied in colourless glass ampoules (type I glass, Ph. Eur.) containing 10 ml
Pack sizes: packs of 10 ampoules

## 6.6 Special precautions for disposal

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.

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.

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

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

## 7 MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Strasse 1
34212 Melsungen, Germany

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 03551/0041

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11.3.2002/31.05.2006

## 10 DATE OF REVISION OF THE TEXT

31/07/2024