PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTOMVI™

Etomidate Injection USP

Solution, 2 mg/mL, Intravenous

General Anesthetic

SteriMax Inc.
2770 Portland Dr.
Oakville, ON L6H 6R4

Date of Initial Approval:
July 14, 2020

Submission Control No: 231245

RECENT MAJOR LABEL CHANGES

Not applicable.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TOMVI™ is indicated for use in health care settings by appropriately trained health care providers in the fields of emergency medicine or anesthesia for:

- The induction of general anesthesia
- The supplementation of subpotent anesthetic agents during anesthesia for short operative procedures such as dilation and curettage or cervical conization.

1.1 Pediatrics (< 18 years)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TOMVI™ in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥ 65 years of age):

Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. Reduced doses of TOMVI™ should be considered based on the physical condition of the patient **(See WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment)**.

2 CONTRAINDICATIONS

TOMVI™ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

TOMVI™ is contraindicated when sedation or general anesthesia are contraindicated.

2.1.1 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Intravenous TOMVI™ should be administered only by persons trained in the administration of general anesthetics and in the management of complications encountered during the conduct of general anesthesia.

ADRENAL SUPPRESSION and use in CRITICALLY ILL Patients

Due to the risks of prolonged suppression of endogenous cortisol and aldosterone production from etomidate, TOMVI™ is not intended for administration by prolonged infusion.

Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels.

TOMVI™ should be used with caution in critically ill patients, including patients with sepsis, as etomidate has been associated with an increased risk of mortality in some studies in such patients **(See also WARNINGS AND PRECAUTIONS; Endocrine and Metabolism and ADVERSE REACTIONS; Post-Market Adverse Drug Reaction)**.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors including pre-induction and concomitant medications, age, ASA status and level of debilitation of the patient. In heavily premedicated patients, both the induction and maintenance doses should be reduced.

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

Convulsions may occur in unpremedicated patients.

3.2 Recommended Dose and Dosage Adjustment

The recommended dose for induction of anesthesia in adult patients is 0.2 mg/kg to 0.4 mg/kg of bodyweight, and must be individualized in each case. The usual dosage is 0.3 mg/kg, injected over a period of 30 to 60 seconds. Geriatric patients may require reduced doses.
Do not exceed a total dose of 30 mL.

Smaller increments of intravenous TOMVI™ may be administered to adult patients during short operative procedures to supplement subpotent anesthetic agents, such as nitrous oxide. The dosage employed under these circumstances, although usually lower than the original induction dose, must be individualized. There are insufficient data to support the use of TOMVI™ for longer procedures, therefore, such use is not recommended.

The use of intravenous fentanyl and other neuroactive drugs employed during the conduct of anesthesia may alter the TOMVI™ dosage requirements. Consult the prescribing information for all other such drugs before using.

In patients who have already received neuroleptic, opiate or sedative agents, the dose of TOMVI™ may need to be reduced and titrated to effect.

Geriatrics (≥65 years of age)
TOMVI™ should be used with caution in geriatric patients, since the potential exists for decreases in cardiac output, which have been reported with doses greater than recommended. A dose of 0.15-0.2 mg/kg of bodyweight should be given and the dose should be further adjusted according to the individual patient response and to clinical effects.

Pediatrics (<18 years)
Health Canada has not authorized an indication for pediatric use.

3.3 Administration

TOMVI™ is for intravenous use. Injections of TOMVI™ should be given slowly (e.g. 10 mL over 30 to 60 seconds).

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

Do not use product if solution shows haziness, particulate matter, discolouration, or leakage.

3.4 Reconstitution

No dilution is necessary before use.

4 OVERDOSAGE

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by a fall in blood pressure.

Overdosage is likely to result in prolonged anesthesia with the possibility of respiratory depression, apnea, or respiratory arrest, in which case adequate respiratory support is critical. Hypotension has been observed. Prolonged adrenal suppression may also occur with overdosage. Overdosage may be associated

with disorientation and delayed awakening.

Treatment:

In the event of suspected or apparent overdosage, the drug should be discontinued, a patent airway established (intubate, if necessary) or maintained, and oxygen administered with assisted ventilation, if necessary.

General supportive measures and close observation are recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	2 mg/mL etomidate solution	Propylene glycol 35% v/v and Water for Injection

TOMVI™ is supplied as a sterile, clear, colourless solution in 10 mL or 20 mL single-use vials in packages of 10 vials.

6 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

For use in induction or supplementation of anesthesia for surgical/diagnostic procedures, TOMVI™ should only be administered by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedures. Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

Because of the hazards of prolonged suppression of endogenous cortisol and aldosterone production, this formulation is not intended for administration by prolonged infusion (see **Endocrine and Metabolism**, **ADVERSE REACTIONS**, **Abnormal Laboratory Findings**).

Transient venous pain on injection may be observed during the administration of etomidate, especially when it is injected into a small vein. The observation of venous pain does not seem to be associated with a higher incidence of thrombosis or thrombophlebitis at the injection site. This venous pain related to injection may be avoided or decreased by intravenous application of a small dose of suitable opioids, e.g.

fentanyl, 1 to 2 minutes before induction.

Driving and Operating Machinery

TOMVI™ 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 TOMVI™.

Cardiovascular

Hypertension, hypotension, tachycardia, bradycardia and other arrhythmias have occasionally been observed during induction and maintenance of anesthesia.

Induction with TOMVI™ may be accompanied with a slight and transient drop in blood pressure due to a reduction of the peripheral vascular resistance.

Geriatric patients, in particular those with hypertension, may be at increased risk for development of cardiac depression following TOMVI™ administration. In frail geratric patients' the potential exists for decreases in cardiac output.

Etomidate administration has been studied in patients with low ejection fraction undergoing elective coronary artery bypass graft surgery. In one randomized active controlled trial of 81 patients with ischemic left ventricular dysfunction (Ejection Fraction <40%) undergoing coronary artery bypass graft surgery with American Society of Anesthesiologists (ASA) physical status class II and III, patients were given etomidate at induction and were compared to those receiving ketofol. Both groups had a relative decrease at induction in hemodynamic parameters (HR, BP, MAP) compared to baseline values.

Endocrine and Metabolism

A single induction dose of etomidate has been associated with a reduction in plasma cortisol and aldosterone concentrations (see **ADVERSE REACTIONS**). For patients undergoing severe stress, particularly those with adrenocortical dysfunction, supplementation with exogenous cortisol should be considered.

TOMVI™ should be used with extreme caution in patients with underlying cortico-adrenal insufficiency and in patients with critical illness, including those with sepsis, as etomidate has been associated with in increased risk of mortality in some studies in such patients (see **Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information).**

Prolonged suppression of endogenous cortisol and aldosterone may occur as a direct consequence of TOMVI™ when given by continuous infusion or in repeated doses. Use of TOMVI™ for maintenance of anesthesia should therefore be avoided. In such situations, stimulation of the adrenal gland with adrenocorticotropic hormone (ACTH) is not useful.

Gastrointestinal

Postoperative nausea and vomiting have been reported following induction with etomidate with a large range in reported incidence (10-75%). Patients who received etomidate combined with a benzodiazepine or propofol appeared to have a lower incidence of nausea and vomiting in several small studies.

Hepatic

In patients with liver cirrhosis, the dose of TOMVI™ should be reduced and titrated to effect.

Neurologic

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 and are often described as myoclonic movements. They may be largely prevented by the intravenous administration of small doses of fentanyl, with diazepam 1-2 minutes before induction with TOMVI™.

In a randomized active controlled trial etomidate was compared to propofol and thiopentone for induction and sedation prior to electroconvulsive therapy. A total of 90 patients were randomized into three groups. Seizure duration was longer with etomidate compared to both thiopentone and propofol ($p<0.0001$).

Etomidate induction is associated with a transient 20-30% decrease in cerebral blood flow. This reduction in blood flow appears to be uniform in the absence of intracranial space occupying lesions. As with other intravenous induction agents, reduction in cerebral oxygen utilization is roughly proportional to the reduction in cerebral blood flow. In patients with and without intracranial space occupying lesions, etomidate induction is usually followed by a moderate lowering of intracranial pressure, lasting several minutes. All of these studies avoided hypercapnia. Information concerning regional cerebral perfusion in patients with intracranial space occupying lesions is too limited to permit definitive conclusions.

Renal

Etomidate is known to be excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because geriatric patients may be more likely to have decreased renal function, dose selection should be done carefully and it may be useful to monitor renal function in those with altered creatinine clearance.

Respiratory

When TOMVI™ is used, resuscitation equipment should be readily available to manage respiratory depression and the possibility of apnea. Hyperventilation, hypoventilation, apnea of short duration (<90 seconds), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients.

Sexual Health

Fertility

There are no data on the effect of etomidate on fertility in humans. Animal studies showed no effects on reproductive function or fertility (see **NON-CLINICAL TOXICOLOGY**).

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate and well-controlled studies on the use of etomidate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see **NON-CLINICAL TOXICOLOGY**).

In animal studies, an increase in still-born fetuses and decrease of pup survival was noted at all doses tested in a study where pregnant rats received etomidate via IV injection during gestation and throughout lactation (GD 16 through Lactation Day 21).

TOMVI™ should not be used during pregnancy unless the potential benefits justify the risks to the fetus.

During obstetric anesthesia etomidate crosses the placenta. In animal studies, etomidate is shown to rapidly cross sheep placenta and reach the fetus in high amounts; however, there was no evidence of cumulative effects of the drug in the fetus as fetal etomidate elimination was as rapid as in the dams (see **NON-CLINICAL TOXICOLOGY**). The Apgar scores of neonates whose mothers received etomidate were 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 neonates after the mothers were given etomidate. The decreased values remained within the normal range.

Published studies in animals demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis (see **NON-CLINICAL TOXICOLOGY**).

6.1.2 Breastfeeding

Etomidate has been identified in breast milk up to 2 hours following administration. The effect of etomidate on neonates is unknown. Breastfeeding should be discontinued during treatment and for a period of approximately 24 hours after treatment with TOMVI™.

6.1.3 Pediatrics (< 18 years)

No sufficient data has been made available to Health Canada by the sponsor; therefore, Health

Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics (≥ 65 years of age)

Clinical data indicates that etomidate may reduce cardiac output in geriatric patients, particularly those with hypertension. Geriatric patients may require lower doses of TOMVI™ than younger patients. Age related differences in pharmacokinetic parameters have been observed in clinical studies. See **WARNINGS AND PRECAUTIONS, Renal and Hepatic**.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The most frequent adverse events that occurred in patients who received etomidate for induction included muscle movements (myoclonus), pain on injection, nausea and vomiting.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A double-blind randomized controlled trial in the United Kingdom enrolled 100 adult patients (65 male, 35 female) scheduled for outpatient cystoscopy. Patients were randomized to receive either 0.3 mg/kg etomidate or 1.5 mg/kg methohexitone for the procedure with the anesthetist blinded to the drug administered. Adverse events for this study are listed in Table 2. Anesthesia was maintained with 1% halothane in 66% nitrous oxide and oxygen.

Table 2 - Adverse events in patients undergoing cystoscopy

	Etomidate n = 50 (%)	**Methohexitone n = 50 (%)**
General disorders and administration site conditions		
Injection site pain	2 (4)	3 (6)
Nervous system disorders		
Myoclonus	11 (22)	0
Respiratory disorders		
Apnea	0	0

Cough	2 (4)	9 (18)

Note: Causality of adverse events was not reported.

A double-blind randomized controlled trial conducted in Canada enrolled 48 patients undergoing minor gynaecological procedures. Patients were randomized to receive either 0.3 mg/kg etomidate or 75 mcL/kg alfathesin as intravenous induction agents. Adverse events for this study are listed in Table 3. Additional increments of etomidate or alfathesin were injected at 25% of induction dose if patients moved in response to surgical stimulus.

Table 3 - Adverse events in patients undergoing minor gynaecological operations

	Etomidate n = 24 (%)	**Alfathesin n = 24 (%)**
Gastrointestinal disorders		
Nausea and/or vomiting	9 (38)	2 (8)
General disorders and administration site conditions		
Injection site pain	10 (42)	0
Nervous system disorders		
Dyskinesia	12 (50)	6 (25)
Respiratory disorders		
Apnea	5 (21)	9 (38)

Note: Causality of adverse events was not reported.

Pain on injection was seen in 10 patients, all of whom received etomidate. This was more frequent in patients receiving etomidate into a hand vein (57%) versus an arm vein (20%) but this difference was not statistically significant.

The incidence of apnoea following induction was higher in the alfathesin group, but the mean apneic period was longer with etomidate (42.4 ±25.3 seconds) than with alfathesin (19.9±9.3 seconds). Involuntary movements occurred more frequently following etomidate than alfathesin. Respiratory disturbances comprising hiccough, coughing, and mild laryngospasm occurred with similar incidence in both groups. In the recovery room, nine patients (38%) vomited after etomidate compared to two (8%) after alfathesin.

After discharge from hospital, the two groups were comparable in terms of vomiting (etomidate: 16%, alfathesin: 6%) and drowsiness (etomidate: 58%, alfathesin: 39%).

A double-blind randomized controlled trial in China enrolled 240 female patients undergoing surgical

abortion. Patients were randomized to receive 0.2 mg/kg etomidate (E), 0.2 mg/kg etomidate and 1 mcg/kg fentanyl (EF), 0.2 mg/kg etomidate with 1 mcg/kg fentanyl and 0.02 mg/kg midazolam (EFM), 2 mg/kg propofol (P), 2 mg/kg propofol and 1 mcg/kg fentanyl (PF), or 2 mg/kg propofol with 1 mcg/kg fentanyl and 0.02 mg/kg midazolam (PFM; N=40 each). If a patient had spontaneous movements that hampered the surgical procedure an additional 1 to 2 mL bolus dose of 2 mg/kg propofol or 0.2 mg/kg etomidate (group dependent) was administered. Adverse events are listed in Table 4.

Table 4 - Adverse events in patients undergoing surgical abortion

	E n=40 (%)	**EF n=40 (%)**	**EFM n=40 (%)**	**P n=40 (%)**	**PF n=40 (%)**	**PFM n=40 (%)**
Gastrointestinal disorders						
Nausea and vomiting	23 (57.5)	20 (50)	9 (22.5)	0	1 (2.5)	0
General disorders and administration site conditions						
Injection site pain	6 (12.5)	0	6 (12.5)	29 (72.5)	24 (60)	32 (80)
Nervous system disorders						
Myoclonus	18 (45)	24 (60)	13 (32.5)	3 (7.5)	1 (2.5)	1 (2.5)

E=etomidate; EF=etomidate and fentanyl; EFM=etomidate, fentanyl, and midazolam; P=propofol; PF= propofol and fentanyl; PFM= propofol, fentanyl, and midazolam

There was a significant difference in the incidence of injection-induced pain in the propofol groups and the etomidate groups. Twenty-nine, 24 and 32 out of 40 patients in groups P, PF and PMF, respectively (72.5%, 60% and 80%), complained of injection-induced pain vs. 6, 0 and 6 out of 40 in the E, EF and EMF groups, respectively (12.5%, 0% and 12.5%). There were no significant differences in pain levels amongst the three groups of propofol or etomidate.

Myoclonus and postoperative nausea and vomiting were lower in the propofol groups than in the etomidate groups. Three, one and one out of 40 patients in groups P, PF and PMF, respectively (7.5%, 2.5% and 2.5%), recorded myoclonus vs. 18, 24 and 13 out of 40 in the E, EF and EMF groups, respectively (45%, 60% and 32.5%). Zero, one and zero out of 40 patients in groups P, PF and PMF, respectively (0%, 2.5% and 0%), recorded nausea and vomiting vs. 23, 20 and 9 out of 40 in the E, EF and EMF groups, respectively (57.5%, 50% and 22.5%). There were no significant differences in incidence of myoclonus and postoperative nausea and vomiting amongst the three propofol groups. The incidences of myoclonus and postoperative nausea and vomiting in group EMF (32.5% and 22.5%) were lower than those in groups E (45.0% and 57.5%) and EF (60% and 50%).

Data from 4 open label clinical trials of etomidate provided safety information on 812 subjects

undergoing induction of general anesthesia; all subjects took at least one dose of etomidate. 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 injection vein pain (7.6).

Table 5 displays ADRs (including those mentioned above) that have been reported with the use of etomidate from either clinical trial or post-marketing 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 5 - Adverse drug reactions rates in subjects receiving etomidate for induction in open-label studies and in post-marketing use

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)	**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 tachycardia	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	

7.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Postoperative epinephrine and norepinephrine levels significantly increased relative to baseline in patients receiving etomidate. Catecholamine levels returned to baseline 6 hours postoperatively.

Three studies assessed adrenocortical function following administration of 0.3 mg/kg etomidate. Following administration, cortisol levels were significantly reduced in subjects treated with etomidate, ranging between 30% to 60% of baseline levels. Cortisol levels returned to baseline after 20 hours.

Postoperative aldosterone levels were significantly lower relative to baseline in patients who received etomidate. Aldosterone levels remained significantly lower than baseline for over 20 hours postoperatively.

7.4 Post-Market Adverse Reactions

Adrenal Suppression and use in Critically Ill Patients

Post-marketing ADRs are displayed in Table 5 (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

Clinical and preclinical studies show that a single dose of etomidate suppresses the adrenal response to ACTH. This transient adrenal insufficiency has been shown to occur in all patients mainly through inhibition of 11β-hydroxylase resulting in decreased cortisol levels. Based on the results of several studies and meta-analyses investigating the effects of etomidate on morbidity and mortality in various patient populations, an association between adrenal suppression caused by etomidate use and an increased risk of morbidity and mortality in critically ill patients, including those with sepsis, cannot be ruled out. Therefore, etomidate should be used with caution in critically ill patients, including patients with sepsis (See **SERIOUS WARNINGS AND PRECAUTIONS BOX, and WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

8 DRUG INTERACTIONS

8.1 Overview

The hypnotic effect of TOMVI™ may be enhanced by neuroleptic drugs, opioids, sedatives and alcohol. Induction with TOMVI™ may be accompanied by a slight and transient reduction in peripheral resistance which may enhance the effect of other drugs thereby reducing blood pressure. TOMVI™ is

pharmacologically compatible with muscle relaxants, premedication drugs and inhalation anesthetics in current clinical use.

8.2 Drug-Drug Interactions

Fentanyl / alfentanil – When administered with fentanyl IV 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 TOMVI™ is co-administered with fentanyl IV, the dose may need to be reduced.

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 concentration of etomidate may drop below the hypnotic threshold.

8.3 Drug-Food Interactions

Interactions with specific foods have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The production of sedation and hypnosis by etomidate is thought to occur through enhancement of the function of gamma-aminobutyric acid type A ($GABA_A$) receptors in the brain. Specifically, etomidate increases the potency with which GABA activates $GABA_A$ receptors and can directly activate the receptors in the absence of GABA. Etomidate interacts selectively with $GABA_A$ receptors that contain β2 or β3 subunits.

9.2 Pharmacodynamics

Etomidate is a general anesthetic without analgesic activity. Intravenous injection of etomidate produces anesthesia characterized by a rapid onset of action, usually within one minute. Duration of anesthesia is dose dependent but relatively brief, approximately 7 minutes, with a quick recovery after regaining consciousness.

The most characteristic effect of intravenous etomidate on the respiratory system is apnea.

Reduced cortisol plasma levels have been reported with induction doses of 0.3 mg/kg etomidate. These persist for approximately 6 to 8 hours and return to baseline within 24 hours.

Data suggests that etomidate can lower intraocular pressure.

9.3 Pharmacokinetics

Table 6 - Summary of TOMVI™ Pharmacokinetic Parameters in Patients Undergoing Surgery

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	CL (mL/kg•min)	Vd (L/kg)
Single dose mean	322.6	0.067	3 to 5	11.7	4.5

Absorption: 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, and is rapidly distributed to the brain and other tissues. Its volume of distribution is about 4.5 L/kg

Metabolism: Etomidate is rapidly metabolized in plasma and in the liver to etomidate carboxylic acid.

Elimination: 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.

Special Populations and Conditions

Geriatrics: Reduced protein binding, decreased initial distribution volumes and lower total clearance is seen in geriatric patients; this may necessitate lower etomidate dosing.

10 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C to 30°C). For single use only. Unused portions of each vial must be discarded properly. Do not save any unused portions for later administration.

11 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

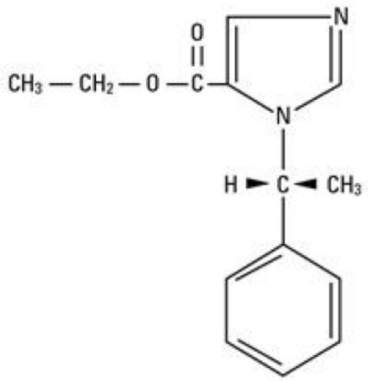
Drug Substance

Proper name: Etomidate

Chemical name: (R)-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate

Molecular formula and molecular mass: $C_{14}H_{16}N_2O_2$, 244.289 g/mol

Structural formula:



Physicochemical properties: A white or almost white powder that is insoluble in water, freely soluble in alcohol and in methylene chloride.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials in patients undergoing short surgical procedures

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Milller *et al*., 1978	Double-blind randomized controlled trial	Group 1: 0.3 mg/kg of intravenous etomidate. Group 2: 1.5 mg/kg of intravenous methohexitone:	100	Group 1: 56.83±2.7 years Group 2: 56.3±2.75 years	Group 1: 33M/17F Group 2: 32M/18F
Morison *et al*., 1982	Double-blind randomized controlled trial	Group 1: 0.3 mg/kg of intravenous etomidate. Group 2: 75 mcL/kg of intravenous alfathesin.	48	Group 1: 23.7±1.4 years Group 2: 23.0±1.2 years	24F per group
Wu *et al*., 2013	Double-blind randomized controlled trial	Group 1: 0.2 mg/kg etomidate Group 2: 0.2 mg/kg etomidate + 1 mcg/kg fentanyl Group 3: 0.2 mg/kg etomidate + 1 mcg/kg fentanyl + 0.02 mg/kg midazolam Group 4: 2 mg/kg propofol Group 5: 2 mg/kg	240	Group 1: 27.1±5.0 years Group 2: 29.5±6.3 years Group 3: 27.7±5.8 years Group 4: 27.1±4.0 years	40F per group

		propofol + 1 mcg/kg fentanyl Group 6: 2 mg/kg propofol + 1 mcg/kg fentanyl + 0.02 mg/kg midazolam		Group 5: 28.4±6.2 years Group 6: 28.2±5.0 years	

F=female; M=male

The patient populations in the three studies consisted predominantly of female patients with two of the studies only including females while one study was predominantly (65%) male patients. The mean age of patients in the studies ranged from 23.0 to 56.8 years with mean weight ranging from 51.5 to 66.7 kg. The surgical procedures included cystoscopy, minor gynaecological operations, and surgical abortion. Other demographic data were not provided, although one study was conducted in Canada, one study in the United Kingdom, and one study in China.

13.2 Study Results

Miller *et al.,* 1978

This double-blind randomized controlled trial conducted in the United Kingdom enrolled 100 adult patients (65 male, 35 female) scheduled for outpatient cystoscopy. Patients were randomized to receive either 0.3 mg/kg etomidate or 1.5 mg/kg methohexitone for the procedure with the anaesthetist blinded to the drug administered. Systemic arterial pressure and heart rate were measured prior to induction, immediately after induction, and on recovery. Patient recovery times were also recorded. Anesthesia was maintained with 1% halothane in 66% nitrous oxide and oxygen.

Overall, recovery times did not significantly differ between etomidate and methohexitone.

Table 8 Results of Miller *et al*., 1978 study patients undergoing cystoscopy

Endpoint	Etomidate (n=50)	Methohexitone (n=50)	P-value
Time to recover from anesthesia (minutes)	4.6±0.3	3.8±0.28	NS

NS=non-significant

Morison *et al.,* 1982

This double-blind randomized controlled trial conducted in Canada enrolled 48 patients undergoing minor gynaecological operations. Patients were randomized to receive either 0.3 mg/kg etomidate or 75 mcL/kg alfathesin as intravenous induction agents. Loss of response, loss of eyelash reflex, duration of anesthesia, recovery times, heart rate, and blood pressure were measured. Additional increments of

etomidate or alfathesin were injected at 25% of induction dose if patients moved in response to surgical stimulus.

There were no differences between groups in terms of time for loss of response (etomidate: 50.9±1.8 seconds; alfathesin: 45.7±2.1 seconds), loss of eyelash reflex (etomidate: 77.3±5.7 seconds; alfathesin: 62.2±2.5 seconds), and duration of anesthesia (etomidate: 8.8±1.1 min; alfathesin: 8.3±0.9 min).

Recovery times for the two groups were not significantly different for eyes open (etomidate: 2.83±0.42 min; alfathesin: 2.87±0.35 min), giving date of birth (etomidate: 5.23±0.68 min; alfathesin: 5.76±0.60 min), and being "street fit" (etomidate: 3.30±0.15 hours; alfathesin: 3.25±0.15 hours).

Table 9 - Results of Morison *et al*., 1982 study patients undergoing minor gynecological operations

Endpoint	Etomidate (n=24)	Alfathesin (n=24)	P-value
Time until loss of response (seconds)	50.9±1.8	45.7±2.5	NS
Time until loss of eyelash reflex (seconds)	77.3±5.7	62.2±2.5	NS
Duration of anesthesia (minutes)	8.8±1.1	8.3±0.9	NS
Time until eyes open (minutes)	2.83±0.42	2.87±0.35	NS
Time to recall birth date (minutes)	5.23±0.68	5.76±0.60	NS
Time until street fit (hours)	3.30±0.15	3.25±0.15	NS

NS=non-significant

Wu *et al.,* 2013

This double-blind randomized controlled trial in China enrolled 240 female patients undergoing surgical abortion. Patients were randomized to receive 0.2 mg/kg etomidate (E), 0.2 mg/kg etomidate and 1 mcg/kg fentanyl (EF), 0.2 mg/kg etomidate with 1 mcg/kg fentanyl and 0.02 mg/kg midazolam (EFM), 2 mg/kg propofol (P), 2 mg/kg propofol and 1 mcg/kg fentanyl (PF), or 2 mg/kg propofol with 1 mcg/kg fentanyl and 0.02 mg/kg midazolam (PFM; N=40 each). Recovery times, respiratory and cardiovascular measures, and adverse events were assessed throughout. If a patient had spontaneous movements that hampered the surgical procedure a 1 to 2 mL bolus dose of 2 mg/kg propofol or 0.2 mg/kg etomidate (group dependent) was supplemented.

The mean time to eye opening in group PF was significantly shorter than that in group PFM (4.5±1.7 min vs. 6.0±2.5 min, p=0.026). In addition, the mean time to obeying commands achieved in group PF (4.6±1.7 min) was significantly shorter than that in groups P (5.7±1.6 min, p=0.042) and PFM (6.2±2.4 min, p=0.016). The mean PACU recovery time in group PF was significantly shorter than that in group P

(11.8±2.7 min vs. 13.9±3.2 min, p=0.047). Recovery times for eye opening, obeying commands, and PACU recovery time were not significantly different in the etomidate groups.

Recovery times for etomidate and propofol were similar and recovery time was not influenced by fentanyl or midazolam in the etomidate group. The addition of fentanyl and midazolam in the etomidate group increased the duration until a supplementary dose was needed.

Table 10 - Results of Wu *et al*., 2013 study patients undergoing surgical abortion

Endpoint	Group P (n=4)	Group PF (n=4)	Group PFM (n=4)	Group E (n=4)	Group EF (n=4)	Group EFM (n=4)
Time to eye opening (minutes)	4.7±1.2	4.5±1.7	6.0±2.5[b]	5.2±5.1	5.4±2.1	4.6±2.1
Time to obeying commands (minutes)	5.7±1.6[b]	4.6±1.7[a]	6.2±2.4[b]	5.1±3.1	5.8±2.3	4.7±2.2
PACU recovery time	13.9±3.2[b]	11.8±2.7[a]	12.7±4.3	12.0±5.7	13.6±5.0	12.8±5.0

[a]p<0.05 differences between groups P and PF.
[b]p<0.05 differences between groups PF and P, and between groups PF and PMF
E=etomidate; EF=etomidate and fentanyl; EFM=etomidate, fentanyl, and midazolam; P=propofol; PACU=post-anesthesia care unit; PF=propofol and fentanyl; PFM=propofol, fentanyl, and midazolam
Data are mean±SD. One-way ANOVA determined significant differences.

14 NON-CLINICAL TOXICOLOGY

General Toxicology

Etomidate is a potent IV hypnotic in mice, rats, guinea-pigs, rabbits and dogs with ED_{50}'s for hypnosis varying from 0.14 mg/kg in guinea-pigs to 1.02 mg/kg in mice. In rats, ED_{50}'s for hypnosis varied (0.57 to 1.11 mg/kg) based on weight (100 g vs. 200 g) and how quickly etomidate was injected (fast vs. slow), with hypnosis occurring at lower concentrations of etomidate at higher weights and following fast injection. In dogs and rabbits, the ED_{50}'s were 0.48 mg/kg and 0.50 mg/kg, respectively. Duration of hypnosis in all species is dose-dependent and recovery is very rapid. Following 5 minutes of hypnosis, complete recovery was observed within 8.3 minutes after injection in rabbits, within 11 minutes in guinea-pigs, within 14 minutes in dogs, within 31 minutes in mice, and within 20 to 28 minutes in rats. The safety ratio (LD_{50}/ED_{50}) of etomidate is very high across species with the ratio being 50.0 in guinea-pigs, 29.0 in mice, from 19.8 to 31.7 by rapid and from 20.5 to 28.3 by slow injection in rats, 24.0 in rabbits, and 15.9 in dogs. In rats of different body weights, it appears that etomidate is more potent (ED_{50} range: 0.57 to 0.75 mg/kg) and slightly more toxic (LD_{50} range: 14.8 to 18.5 mg/kg) when injected rapidly than when injected slowly (ED_{50} range: 0.88 to 1.11 mg/kg; LD_{50} range: 22.8 to 26.1 mg/kg).

Repeat-dose studies were conducted in rats and dogs. No mortality was noted in either rats or dogs. Rats were administered 0, 0.31, 1.25 or 5 mg/kg/day for 21 days, and dogs 0, 0.25, 0.75 or 1.5 mg/kg/day for 14 days. In female rats, a decrease in food consumption was noted at doses of 1.25 and 5 mg/kg/day and in male rats a decrease in absolute and relative weight of the spleen was noted. In dogs, at doses of 0.75 and 1.5 mg/kg/day, myoclonic contractions, muscle tremors, vomiting and defecation was occasionally observed. Ataxia was observed at all dose levels in dogs and rats.

Etomidate has been shown to affect steroidogenesis in animals; specifically, cortisol, aldosterone, and testosterone.

Published studies in animals demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis.

Genotoxicity

Studies to evaluate the mutagenic potential of etomidate have not been completed.

Carcinogenicity

Long-term animal studies to evaluate the carcinogenic potential of etomidate have not been completed.

Reproductive Toxicity

Fertility

In a fertility and early embryonic development study in which male and female rats were treated intravenously with 0.31, 1.25, or 5 mg/kg/day etomidate prior to mating, no adverse effects on fertility were noted.

Embryo-fetal Development

Repeated doses of etomidate administered to rats from gestation day (GD) 6 through GD 15 had no adverse effects on average litter size, number of implantations, proportions of live, dead, and resorbed fetuses, and fetal body weights up to 5.00 mg/kg/day. At 5 mg/kg/day, 2 fetuses had waved ribs; however, this was not considered treatment-related due to regular encounters within control groups.

Repeated doses of etomidate administered to rabbits from gestation day (GD) 6 through GD 18 had no adverse effects on average litter size, number of implantations, proportions of live, dead, and resorbed fetuses, and fetal body weights up to 4.50 mg/kg/day. At 4.50 mg/kg/day, 1 fetus had fused ribs; however, this was not considered treatment-related due to regular encounters within control groups.

Administration of isoflurane or propofol over a 5-hour period on GD 120 (with respect to brain development, this corresponds to the 3rd trimester of gestation in humans) or in 6-day old primates, as

well as administration of ketamine for 24 hours on GD122, resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

Pre- and Post-natal Development

Increased still born fetuses and decreased pup survival were noted at all doses tested in a study where pregnant rats received etomidate via IV injection during gestation and throughout lactation (GD 16 through Lactation Day 21) at dose levels of 0.31, 1.25, or 5 mg/kg/day etomidate. These doses also produced maternal toxicity (decreased food consumption and increased mortality).

In sheep studies, etomidate is shown to rapidly cross the placenta and reach the fetus after a 1 mg/kg IV bolus dose and one-hour infusion of 100 µg/kg/min. After a single IV bolus dose the AUC ratio between the fetus and mother showed a value of 0.45 ± 0.32, and after a one-hour infusion 0.37 ± 0.08. Although etomidate crosses the placenta very rapidly and reaches the fetus in high amounts, there was no evidence of cumulative effects of the drug in the fetus.

Studies in Juvenile Animals

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as etomidate, that either block N-methyl-D-aspartate (NMDA) receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately 3 years of age in humans.

Other Toxicity

A local irritation study was conducted with high concentrations of etomidate in New Zealand white rabbits. High concentrations of etomidate sulphate were injected into the ear veins. No irritation was observed at concentrations up to 5 mg/mL. Irritation was observed at 10 mg/mL; however, this was reversible, resolving within 24 to 96 hours following injection. At 20 and 40 mg/mL, severe irritation was observed followed by necrosis in all treated ears.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

TOMVI™
Etomidate Injection USP, 2 mg/mL

Read this carefully before you start taking **TOMVI™**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TOMVI™**.

Serious Warnings and Precautions

ADRENAL SUPPRESSION in seriously or critically ill patients:

TOMVI™ decreases your adrenal glands ability to make cortisol, a stress hormone in your body, for short periods of time. You should not use TOMVI™ if you have adrenal suppression.

Your doctor may not use TOMVI™ if you are critically ill with a severe blood infection or in a shock state. It is not clear if TOMVI™ might cause increased death in critically ill patients.

What TOMVI™ used for?

TOMVI™ is an anesthetic that is used in adults:

- to help make you asleep (unconscious) for a surgery or other medical procedure.
- with other anesthetics to help keep you asleep for a short surgery.

How does TOMVI™ work?

TOMVI™ works in the brain to cause you to be asleep (unconscious). It is a short-acting anesthetic and patients can have a quick recovery after waking up.

What are the ingredients in TOMVI™?

Medicinal ingredient: Etomidate
Non-medicinal ingredients: Propylene glycol 35% v/v, Water for injection

TOMVI™ comes in the following dosage forms:

Solution, 2 mg/mL in 10 mL or 20 mL single-use vials

Do not use TOMVI™ if:

- you are allergic to etomidate or to any of the ingredients in TOMVI™.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given TOMVI™. Talk about any health conditions or problems you may have, including if you:

- have heart, lung, kidney, or liver problems or if you have been generally unwell for some time
- have a serious infection in your blood (sepsis)
- have ever had an epileptic fit or convulsion.
- are pregnant, plan to become pregnant. TOMVI™ may cause harm to your fetus if you are pregnant.
- are breastfeeding. If you are breastfeeding, you should not nurse your baby during treatment with TOMVI™ and for 24 hours after.
- have problems with your adrenal glands not working properly
- have low blood pressure
- have been taking strong painkillers for a long time
- have a drinking problem (alcoholism)

Other warnings you should know about:

- You may have pain in your vein when you are being given TOMVI™
- You may have muscle twitches or seizures while you are being given TOMVI™.
- A single dose of TOMVI™ can cause a decrease in your stress hormone called cortisol and another hormone called aldosterone.
- Do not drive or use machines for at least 24 hours after you were given TOMVI™.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TOMVI™:

- Other anesthetics or medicines to calm you down (also called "sedatives")
- Muscle relaxants
- Strong medicines for pain called "opioid analgesics" such as morphine, fentanyl or alfentanil
- Antipsychotic medicines used to improve thoughts, feelings and/or behaviour in patients with conditions such as schizophrenia or bipolar disorder.
- Alcohol

How to take TOMVI™:

TOMVI™ will be given to you by a healthcare professional who is experienced in the use of general anesthetics.

Usual dose:

The usual dose is 0.3 mg/kg; however, your healthcare professional may adjust the dose depending on the surgical procedure and your medical condition.

Overdose:

Your doctor will care for you in the event of an overdose.

What are possible side effects from using TOMVI™?

These are not all the possible side effects you may have when you are given TOMVI™. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported:

Very common (affects more than 1 in 10 people)
- Cortisol (a hormone) decreased
- Aldosterone (a hormone) decreased
- Abnormal movements or muscle twitching

Common (affects less than 1 in 10 people)
- Pain or discomfort along the vein where the injection was given
- Dizziness and fainting. These are signs of lowered blood pressure but are mild and do not usually last long
- Being sick
- Feeling sick
- Breathing stops for a short period of time. If necessary, your breathing will be helped by a machine (ventilator)
- Breathing faster and/or deeper than normal
- Noisy breathing
- Rash
- Nausea and vomiting

Uncommon (affects less than 1 in 100 people)
- Unusual muscle stiffness causing poor control of movement
- Swelling, redness and clotting in a vein, which is extremely tender when touched
- Breathing more slowly or weakly than usual
- Hypertension (high blood pressure)
- Hiccups
- Cough
- Too much saliva
- Redness of the skin
- Complications with the anesthetic

- Delayed recovery from the anesthetic
- Not enough painkiller
- Involuntary movements of the eye
- Heart beating more slowly or extra beats

Other side effects

- Adrenal glands not working properly
- Fits or convulsions
  Difficulty breathing or wheezing which could be fatal
- Shallow, slow or weak breathing
- Dangerous decrease of blood pressure which if untreated may lead to collapse, coma or death
- Heart attack
- Severe allergic reaction
- Heart problems
- Inflammation of the blood vessels
- Rare skin condition, with severe blisters and bleeding in the lips, eyes, mouth, nose and genitals
- Pinkish, itchy swellings on the skin
- Problems using your jaw muscles

You may still have some of these effects when you wake up.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

TOMVI™ will be stored at the hospital or clinic where you are having the surgery or medical procedure.

If you want more information about TOMVI™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this

Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by

SteriMax Inc.
2770 Portland Dr.
Oakville, ON L6H 6R4

Last Revised: July 14, 2020