ETOMIDATE INJECTION
Rx only

DESCRIPTION
Etomidate injection is a sterile, nonpyrogenic solution. Each milliliter contains etomidate, 2 mg, propylene glycol 30%/v/v. The pH is 6.0 (4.0 to 7.0).

It is intended for the induction of general anesthesia by intravenous injection.

The drug etomidate is chemically identified as R(−)(+)-1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid, and has the following structural formula:

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\text{CH}_3\text{CH}(\overset{\text{H}}{\text{C}}\overset{\text{O}}{\text{H}})\overset{\text{H}}{\text{C}}\overset{\text{O}}{\text{H}}\overset{\text{O}}{\text{H}}\]  
Molecular Formula: C_7H_7N_2O_3  
Molecular Weight: 244.3

CLINICAL PHARMACOLOGY
Etomidate is a hypnotic drug without analgesic activity. Intravenous injection of etomidate produces hypnosis characterized by a rapid onset of action, usually within one minute. Duration of hypnosis is dose dependent but relatively brief, usually three to five minutes when an average dose of 0.3 mg/kg is employed. Immediate recovery from anesthesia (as assessed by awakening time, time needed to follow simple commands and time to perform simple tests after anesthesia as well as they were performed before anesthesia), based upon data derived from short operative procedures where intravenous etomidate was used for both induction and maintenance of anesthesia, is as about as rapid as, or slightly faster than, immediate recovery after similar use of thiopental. These same data revealed that the immediate recovery period will usually be shortened in adult patients by the intravenous administration of approximately 0.1 mg of intravenous fentanyl, one or two minutes before induction of anesthesia, probably because less etomidate is generally required under these circumstances (consult the package insert for fentanyl before using).

The most characteristic effect of intravenous etomidate on the respiratory system is a slight elevation in arterial carbon dioxide tension (PACO₂). See also ADVERSE REACTIONS.

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 appear to be unresponsive to ACTH stimulation. This probably represents blockage of 11 beta-hydroxylation within the adrenal cortex.

In clinical studies, elderly patients demonstrated decreased initial distribution volumes and total clearance of etomidate. Protein binding of etomidate to serum albumin was also significantly decreased in these individuals. Reduced plasma cortisol and aldosterone levels have been reported following induction doses of etomidate. These results persist for approximately 6 to 8 hours and appear to be unresponsive to ACTH stimulation. This probably represents blockage of the high frequency of transient skeletal muscle movements (see ADVERSE REACTIONS).

Intravenous etomidate is also indicated for the supplementation of suboptimal anesthetic agents, such as nitrous oxide in oxygen, during maintenance of anesthesia for short operative procedures such as dilation and curettage or cervical conization.

CONTRAINDICATIONS
Etomidate is contraindicated in patients who have shown hypersensitivity to it.

WARNINGS
INTRAVENOUS ETOMIDATE 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. BECAUSE OF THE HAZARDS OF PROLONGED SUPPRESSION OF ENDOGENOUS CORTISOL AND ALDOSTERONE PRODUCTION, THIS FORMULATION IS NOT INTENDED FOR ADMINISTRATION BY PROLONGED INFUSION.

PRECAUTIONS
Do not administer unless solution is clear and container is undamaged. Discard unused portion (see DOSAGE AND ADMINISTRATION).

1. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenesis or mutagenesis studies have been carried out on etomidate. The results of reproduction studies showed no impairment of fertility in male and female rats when etomidate was given prior to pregnancy at 0.31, 1.25 and 5 mg/kg (approximately 1X, 4X and 16X human dosage).

2. Pregnancy Category C. Etomidate has been shown to have an embryocidal effect in rats when given in doses 1 and 4 times the human dose. There are no adequate and well-controlled studies in pregnant women. Etomidate should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. Etomidate has not been shown to be teratogenic in animals. Reproduction studies with etomidate have been shown to:
   a. Decrease pup survival at 0.3 and 5 mg/kg in rats (approximately 1X and 16X human dosage) and at 1.5 and 4.5 mg/kg in rabbits (approximately 5X and 15X human dosage).
   b. Increase slightly the number of stillborn fetuses in rats at 0.3 and 1.25 mg/kg (approximately 1X and 4X human dosage).
   c. Cause maternal toxicity with deaths of 6/20 rats at 5 mg/kg (approximately 16X human dosage) and 6/20 rabbits at 4.5 mg/kg (approximately 15X human dosage).

3. Labor and Delivery: There are insufficient data to support use of intravenous etomidate in obstetrics, including Caesarean section deliveries. Therefore, such use is not recommended.

4. Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when etomidate is administered to a nursing mother.

5. Pediatric Use: There are inadequate data to make dosage recommendations for induction of anesthesia in patients below the age of ten (10) years; therefore, such use is not recommended (see also DOSAGE AND ADMINISTRATION).

6. Geriatric Use: Clinical data indicates that etomidate may induce cardiac depression in elderly patients, particularly those with hypertension (see CLINICAL PHARMACOLOGY and OTHER ADVERSE OBSERVATIONS, Circulatory System).

Elderly patients may require lower doses of etomidate than younger patients. Age-related differences in pharmacokinetic parameters have been observed in clinical studies (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

7. Plasma Cortisol Levels: Induction doses of etomidate have been associated with reduction in plasma cortisol and aldosterone concentrations (see CLINICAL PHARMACOLOGY). These have not been associated with changes in vital signs or evidence of increased mortality; however, where concern exists for patients undergoing severe stress, exogenous replacement should be considered.

ADVERSE REACTIONS
The most frequent adverse reactions associated with use of intravenous etomidate are transient venous pain on injection and transient skeletal muscle movements, including myoclonus:

1. Transient venous pain was observed immediately following intravenous injection of etomidate in about 20% of the patients, with considerable difference in the reported incidence (1.2% to 42%). This pain is usually described as mild to moderate in severity but it is occasionally judged disturbing. The observation of venous pain is not associated with a more usual incidence of thrombosis or thrombophlebitis at the injection site. Pain also appears to be less frequently noted when larger, more proximal arm veins are used and it appears to be more frequently noted when smaller, more distal, hand or wrist veins are employed.

2. Transient skeletal muscle movements were noted following use of intravenous etomidate in about 32% of the patients, with considerable difference in the reported incidence (22.7% to 63%). Most of these observations were judged mild to moderate in severity but some were judged disturbing. The incidence of disturbing movements was less when 0.1 mg of fentanyl was given immediately before induction. These movements have been classified as myoclonic in the majority of cases (74%), but avertin movements (7%), tonic movements (10%), and eye movements (9%) have also been reported. No exact classification is available, but these movements may also be placed into three groups by location:

a. Most movements are bilateral. The arms, legs, shoulders, neck, chest wall, trunk and all four extremities have been described in some cases, with one or more of these muscle groups predominating in each individual case. Results of electromyographic studies suggest that these muscle movements are a manifestation of disinhibition of cortical activity; cortical electromyograms, taken during periods when these muscle movements were observed, have failed to reveal seizure activity.

b. Other movements are described as either unilateral or having a predominance of activity of one side over the other. These movements sometimes resemble a localized response to some stimuli, such as venous pain on injection, in the lightly anesthetized patient (averting movements). Any muscle group or groups may be involved but a predominance of movements of the arm in which the intravenous infusion is started is frequently noted.

c. Still other movements probably represent a mixture of the first two types. Skeletal muscle movements appear to be more frequent in patients who also manifest venous pain on injection.

OTHER ADVERSE OBSERVATIONS
Respiratory System: Hyperventilation, hyperventilation, apnea of short duration (5 to 90 seconds with spontaneous recovery), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients. These conditions were managed by conventional countermeasures.

Circulatory System: Hypertension, hypotension, tachycardia, bradycardia and other arrhythmias have occasionally been observed during induction and maintenance of anesthesia. One case of severe hypotension and tachycardia, judged to be anaphylactoid in character, has been reported.


Geriatric patients, particularly those with hypertension, may be at increased risk for the development of cardiac depression following etomidate administration (see CLINICAL PHARMACOLOGY).

Gastrointestinal System: Postoperative nausea and/or vomiting following induction of anesthesia with etomidate is probably no more frequent than the general incidence. When etomidate was used for both induction and maintenance of anesthesia in short procedures such as dilation and curettage, or when insufficient analgesia was provided, the incidence of postoperative nausea and/or vomiting was higher than that noted in control patients who received thiopental.

OVERDOSE
Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by a fall in blood pressure. No adverse cardiovascular or respiratory effects attributable to etomidate overdose have been reported.

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.

The LD₅₀ of etomidate administered intravenously to rats is 20.4 mg/kg.