Storage/Stability/Compatibility

The concentrate for injection should be stored at room temperature; do not freeze and protect from excessive heat. It is a clear, colorless to light yellow solution. Expiration dates of 3 years are assigned after manufacture.

After diluted to a concentration of 10 mg/mL esmolol HCl is stable (at refrigeration temperatures or room temperature) for at least 24 hours in commonly used IV solutions. Esmolol may be diluted in standard D5, LRS or saline (or combinations thereof) IV fluids. At this concentration it is reportedly physically **compatible** with digoxin, dopamine, fentanyl, lidocaine, morphine sulfate, nitroglycerin, and nitroprusside. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Esmolol HCl Injection: 10 mg/mL in 10 mL vials, 20 mg/mL in 5 mL vials and 100 mL bags, and 250 mg/mL in 10 mL amps; *Brevibloc*® (Baxter); generic; (Rx)

ESTRADIOL CYPIONATE

(ess-tra-***dye***-ole) **ECP®**

HORMONAL AGENT (ESTROGEN)

Prescriber Highlights

- Natural estrogen salt used primarily to induce estrus; has been used as an abortifacient (but rarely recommended today)
- Contraindications: Pregnancy (abortifacient, teratogen); the FDA has stated that the use of ECP in food animals is illegal
- Adverse Effects: In CATS & DOGS: bone marrow toxicity, cystic endometrial hyperplasia, pyometra;
- In male animals, feminization may occur; in females, signs of estrus may occur;
- In CATTLE: Prolonged estrus, genital irritation, decreased milk flow, precocious development, & follicular cysts may develop
- Drug Interactions

Uses/Indications

For mares, indications for the use of estradiol include induction of estrus during the non-breeding or breeding seasons and to enhance the mare's uterine defense mechanism. Estradiol cypionate has historically been used as an abortifacient agent in cattle, cats and dogs. Estrogens are no longer recommended by most theriogenologists for use as an abortifacient in small animals. The FDA stated (April 5, 2006): "The use of ECP in food-producing animals is illegal, and manufacturing and compounding of ECP for such use is illegal."

Pharmacology/Actions

The most active endogenous estrogen, estradiol possesses the pharmacologic profile expected of the estrogen class. Estrogens are necessary for the normal growth and development of the female sex organs and in some species contribute to the development and maintenance of secondary female sex characteristics. Estrogens cause increased cell height and secretions of the cervical mucosa, thickening of the vaginal mucosa, endometrial proliferation, and increased uterine tone.

Estrogens have effects on the skeletal system. They increase calcium deposition, accelerate epiphyseal closure, and increase bone formation. Estrogens have a slight anabolic effect and can increase sodium and water retention.

Estrogens affect the release of gonadotropins from the pituitary gland. This can cause inhibition of lactation, ovulation, and androgen secretion.

Pharmacokinetics

No specific information was located regarding the pharmacokinetics of estradiol in veterinary species. In humans, estrogen in oil solutions after IM administration are absorbed promptly and absorption continues over several days. Esterified estrogens (*e.g.*, estradiol cypionate) have delayed absorption after IM administration. Estrogens are distributed throughout the body and accumulate in adipose tissue. Elimination of the steroidal estrogens occurs principally by hepatic metabolism. Estrogens and their metabolites are primarily excreted in the urine, but are also excreted into the bile where most is reabsorbed from the GI.

Contraindications/Precautions/Warnings

Estradiol is contraindicated during pregnancy as it can cause fetal malformations of the genitourinary system and induce bone marrow depression in the fetus.

Estradiol cypionate should not be used to treat estrogen–responsive incontinence in small animals; other estrogens (DES, conjugated estrogens) are less toxic.

In cases of prolonged corpus luteum in cows, a thorough uterine exam should be completed to determine if endometritis or a fetus is present.

Estradiol is reportedly very toxic (bone marrow) to ferrets.

Adverse Effects

Estrogens have been associated with severe adverse reactions in small animals. In cats and dogs, estrogens are considered toxic to the bone marrow and can cause blood dyscrasias. Blood dyscrasias are more prevalent in older animals and if higher dosages are used. Initially, a thrombocytosis and/or leukocytosis may be noted, but thrombocytopenia/leukopenias will gradually develop. Changes in a peripheral blood smear may be apparent within two weeks after estrogen administration. Chronic estrogen toxicity may be characterized by a normochromic, normocytic anemia, thrombocytopenia, and neutropenia. Bone marrow depression may be transient and begin to resolve within 30–40 days or may persist or progress to a fatal aplastic anemia.

Estrogens may cause cystic endometrial hyperplasia and pyometra. After therapy is initiated, an open-cervix pyometra may be noted 1–6 weeks after therapy.

Estrogens may induce mammary neoplasia.

When used chronically in male animals, feminization may occur. In females, signs of estrus may occur and persist for 7–10 days.

In cattle, prolonged estrus, genital irritation, decreased milkflow, precocious development, and follicular cysts may develop after estrogen therapy. These effects may be secondary to overdosage and dosage adjustment may reduce or eliminate them.

Reproductive/Nursing Safety

Estradiol is contraindicated during pregnancy. In humans, the FDA categorizes this drug as category ***X*** for use during pregnancy (*Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***D*** (*Contraindicated. These drugs have been shown to cause congenital malformations or embryotoxicity*.)

Estrogens have been shown to decrease the quantity and quality of maternal milk.

Overdosage/Acute Toxicity

No reports of inadvertent acute overdosage in veterinary patients were located; see Adverse Effects above.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving estradiol and may be of significance in veterinary patients:

- **AZOLE ANTIFUNGALS** (**fluconazole, itraconazole, ketoconazole**): May increase estrogen levels
- **CORTICOSTEROIDS**: Enhanced glucocorticoid effects may result if estrogens are used concomitantly with corticosteroid agents. It has been postulated that estrogens may either alter the protein binding of corticosteroids and/or decrease their metabolism; corticosteroid dosage adjustment may be necessary when estrogen therapy is either started or discontinued
- **MACROLIDE ANTIBIOTICS** (**erythromycin, clarithromycin**): May increase estrogen levels
- **PHENOBARBITAL**: May decrease estrogen activity if administered concomitantly
- **RIFAMPIN**: May decrease estrogen activity if administered concomitantly
- **ST. JOHN'S WORT**: May decrease estrogen activity if administered concomitantly
- **WARFARIN**: Oral anticoagulant activity may be decreased if estrogens are administered concurrently; increases in anticoagulant dosage may be necessary if adding estrogens

Laboratory Considerations

- Estrogens in combination with progestins (*e.g.*, oral contraceptives) have been demonstrated in humans to increase **thyroxine-binding globulin** (**TBG**) with resultant increases in total circulating thyroid hormone. Decreased T_3 resin uptake also occurs, but free T_4 levels are unaltered. It is unclear if estradiol affects these laboratory tests in veterinary patients.

Doses

- **DOGS:**

  For pregnancy avoidance after mismating:

  Note: This drug is rarely used for this indication today.

  a) 0.02 mg/kg (ECP) IM within 72 hours of mating (Burke 1986)

  b) 0.044 mg/kg (ECP) IM once during 3–5 days of standing heat or within 72 hours of mismating (Woody 1988)

  c) 0.044 mg/kg (ECP), not to exceed 1 mg total dose, IM once administered during estrus or early diestrus (Olson et al. 1986)

- **CATS:**

  For pregnancy avoidance after mismating:

  Note: This drug is rarely used for this indication today.

  a) 0.125–0.25 mg (ECP) IM within 40 hours of mating (Wildt 1986)

  b) 0.125–0.25 mg (ECP) IM within 3–5 days of coitus (Woody 1988)

- **CATTLE:**

  The FDA has stated that the use of ECP in food-producing animals is illegal.

- **HORSES:**

  For induction of estrus during the non-breeding season:

  a) 10 mg estradiol cypionate will result in estrus 2–3 days after treatment (Squires and McKinnon 1987)

  For treatment of mares with estrogen-responsive incontinence:

  a) 4–10 mcg/kg estradiol cypionate IM daily for three days and then every other day. Some mares will improve, but does not "cure." (Schott II and Carr 2003)

  For induction of estrus in mares with "silent heat" during breeding season:

  a) 1 mg estradiol (Squires and McKinnon 1987)

  To enhance the mare's uterine defense mechanism:

  a) 1–2 mg estradiol daily for 3–5 days (Squires and McKinnon 1987)

Monitoring

When therapy is either at high dosages or chronic, see adverse effects for more information. Done at least monthly:

- Packed Cell Volumes (PCV)
- White blood cell counts (CBC)
- Platelet counts; Baseline, one month after therapy, and repeated two months after cessation of therapy if abnormal
- Liver function tests

Chemistry/Synonyms

Estradiol is a naturally occurring steroidal estrogen. Estradiol cypionate is produced by esterifying estradiol with cyclopentanepropionic acid, and occurs as a white to practically white, crystalline powder. It is either odorless or may have a slight odor and has a melting range of 149–153°C. Less than 0.1 mg/mL is soluble in water and 25 mg/mL is soluble in alcohol. Estradiol cypionate is sparingly soluble in vegetable oils.

Estradiol may also be known as: beta-oestradiol, dihydrofolliculin, dihydrotheelin, dihydroxyoestrin, estradiolum, NSC-9895, NSC-20293 (alpha-estradiol), and oestradiol; many trade names are available.

Estradiol Cypionate may also be known as: oestradiol cyclopentylpropionate, oestradiol cypionate, *Delestrogen®*, *Depo-Estradiol®*, *Depogen®*, *Dura-Estrin®*, *ECP®*, *E-Cypionate®*, *Estra-D®*, *Estrace®*, *Estro-Cyp®*, *Estroject®*, *depGynogen®*, *Femtrace®*, or *Gynodiol®*.

Storage/Stability/Compatibility

Estradiol cypionate should be stored in light-resistant containers at temperatures of less than 40°C, preferably at room temperature (15–30°C); avoid freezing.

Commercially available injectable solutions of estradiol cypionate are sterile solutions in a vegetable oil (usually cottonseed oil); they may contain chlorobutanol as a preservative.

It is not recommended to mix estradiol cypionate with other medications.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

There are several estradiol-containing implants for use in beef cattle.

HUMAN-LABELED PRODUCTS:

Estradiol Cypionate in Oil for Injection: 5 mg/mL in 5 mL vials; *Depo-Estradiol®* (Pharmacia); (Rx)

Estradiol Valerate in Oil for Injection: 10 mg/mL, 20 mg/mL & 40 mg/mL in 5 mL vials; *Delestrogen®* (Monarch); (Rx)

Estradiol Tablets: 0.45 mg, 0.5 mg, 0.9 mg, 1 mg, 1.5 mg, 1.8 mg and 2 mg micronized estradiol; *Estrace®* (Warner Chilcott), *Gynodiol®* (Fielding), *Femtrace®* (Warner Chilcott); generic; (Rx)

ETHACRYNIC ACID ETHACRYNATE SODIUM

(eth-a-***krin***-ik) Edecrin®

LOOP DIURETIC

Prescriber Highlights

- Rarely-used loop diuretic similar to furosemide; may have greater ototoxicity & GI effects than furosemide
- Contraindications: Patients with anuria, hypersensitivity, or seriously depleted electrolytes
- Caution: Patients with pre-existing electrolyte or water balance abnormalities, impaired hepatic function, & diabetes mellitus
- Adverse Effects: Fluid & electrolyte abnormalities. Others include ototoxicity, GI distress, hematologic effects, weakness, & restlessness
- Drug Interactions

Uses/Indications

Ethacrynic acid is a loop diuretic that shares the same indications as furosemide (congestive cardiomyopathy, pulmonary edema, hypercalcuric nephropathy, uremia, as adjunctive therapy in hyperkalemia and, occasionally, as an antihypertensive agent). Its use has been largely supplanted in the armamentarium by furosemide for these indications.

Ethacrynic acid may be useful in the treatment of nephrogenic diabetes insipidus as it may cause a paradoxical decrease in urine volume. Other uses include the adjunctive treatment of hypercalcemia and to increase the excretion of bromide in the treatment of bromide toxicity.

Pharmacology/Actions

Ethacrynic acid reduces the absorption of electrolytes in the ascending section of the loop of Henle, decreases the reabsorption of both sodium (to a much greater extent than the thiazides) and chloride, increases the excretion of potassium in the distal renal tubule, and directly effects electrolyte transport in the proximal tubule. The exact mechanisms of ethacrynic acid's effects have not been established. It has no effect on carbonic anhydrase nor does it antagonize aldosterone. Ethacrynic acid increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate.

Pharmacokinetics

Ethacrynic acid is absorbed rapidly and nearly completely from the GI tract. It does not enter the CNS and accumulates in the liver. It is unknown if ethacrynic acid crosses the placenta or enters milk. Ethacrynic acid is metabolized in the liver and also secreted via the proximal tubules into the urine. Serum half-lives in humans averages around one hour. Duration of effect is about 6–8 hours after oral dosing; about 2 hours after IV administration.

Contraindications/Precautions/Warnings

Ethacrynic acid is contraindicated in patients with anuria, are hypersensitive to the drug, or have seriously depleted electrolytes. Ethacrynic acid is also contraindicated in human infants (safety not established).

Ethacrynic acid should be used with caution in patients with pre-existing electrolyte or water balance abnormalities, impaired hepatic function (may precipitate hepatic coma), and diabetes mellitus. Patients with conditions that may lead to electrolyte or water balance abnormalities (*e.g.*, vomiting, diarrhea, etc.) should be monitored carefully.

Adverse Effects

Ethacrynic acid may induce fluid and electrolyte abnormalities. Patients should be monitored for hydration status and electrolyte imbalances (especially potassium, calcium and sodium). Other potential adverse effects include ototoxicity (especially in cats with high dose IV therapy), gastrointestinal disturbances, hematologic effects (anemia, leukopenia), weakness, and restlessness. Ethacrynic acid is thought to have a greater incidence of ototoxicity and GI effects than furosemide.

Reproductive/Nursing Safety

A study where pregnant dogs received 5 mg/kg daily demonstrated no teratogenic effects or effects on the pregnancy. It is unknown whether the drug enters milk. In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

It is unknown if ethacrynic acid is distributed into milk.

Overdosage/Acute Toxicity

The LD_{50} in dogs after oral administration is >1000 mg/kg; after IV injection >300 mg/kg. Chronic overdosing at 10 mg/kg for six months in dogs led to development of calcification and scarring of the renal parenchyma.

Acute overdosage may cause electrolyte and water balance problems, CNS effects (lethargy to coma and seizures) and cardiovascular collapse.

Treatment consists of emptying the gut after recent oral ingestion, using standard protocols. Avoid giving concomitant cathartics as they may exacerbate the fluid and electrolyte imbalances that can occur. Aggressively monitor and treat electrolyte and water balance abnormalities supportively. Additionally, monitor respiratory, CNS, and cardiovascular status; treat supportively and symptomatically, if necessary.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving ethacrynic acid and may be of significance in veterinary patients: