Ethacrynic acid is a potent diuretic which, when given in excessive amounts, may lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule must be adjusted to the individual patient's needs (see DOSAGE AND ADMINISTRATION).

DESCRIPTION
Ethacrynic acid is an unsubstituted ketone derivative of an aryloxyacetic acid. It is designated chemically as [2,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid, and has a molecular weight of 303.14. Ethacrynic acid is a white, or practically white, crystalline powder, very slightly soluble in water, but soluble in most organic solvents such as alcohols, chloroform, and benzene. Its empirical formula is C_{14}H_{12}Cl_{2}O_3 and its structural formula is:

![Structural formula of Ethacrynic acid](image)

Ethacrynic acid is supplied as 25 mg tablets for oral use. The tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, and cellulose. Intravenous Ethacrynic sodium is a sterile freeze-dried powder and is supplied in a vial containing:

- 2000 mg ethacrynic acid
- 550 mg inactive ingredient:
  - Mannitol
  - 62.5 mg

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism
Ethacrynic acid acts on the ascending limb of the loop of Henle and on the proximal and distal tubules. Urinary output is usually dose dependent and related to the magnitude of fluid accumulation. Water and electrolyte excretion may be increased several times over that observed with thiazide diuretics, since ethacrynic acid inhibits reabsorption of a much greater proportion of filtered sodium than most other diuretic agents. Therefore, ethacrynic acid is effective in many patients who have significant degrees of renal insufficiency (see WARNINGS concerning deafness).

Intravenous administration of ethacrynic acid results in little or no effect on glomerular filtration or on renal blood flow, except following pronounced reductions in plasma volume when associated with rapid diuresis.

The ethylene excretion pattern of ethacrynic acid varies from that of the thiazides and the furanuric diuretics. Initial sodium and chloride excretion is usually substantial and chloride loss exceeds that of sodium. With prolonged administration, chloride excretion declines, and potassium and hydrogen ion excretion may increase. Ethacrynic acid is effective whether or not there is clinical dehydration.

Although ethacrynic acid, in carefully controlled studies in animals and experimental subjects, produces a more favorable sodium/potassium excretion ratio than the thiazides, in patients with increased diuresis excessive amounts of potassium may be excreted.

Onset of action is rapid, usually within 30 minutes after an oral dose of ethacrynic acid or within 5 minutes after an intravenous injection of ethacrynic sodium. After oral use, diuresis peaks in about 2 hours and lasts about 6 to 8 hours.

The sulfhydryl binding propensity of ethacrynic acid differs somewhat from that of the organomercurials. Its mode of action is not by carbonic anhydrase inhibition. Ethacrynic acid does not cross the blood-brain barrier.

INDICATIONS AND USAGE
Ethacrynic acid is indicated for treatment of edema when an agent with greater diuretic potential than those commonly employed is required.

1. Treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

2. Short-term management of ascites in patients, particularly older patients, with severe myocardial disease who have been receiving diuretics and presumably retain sodium and water, with or without accompanying hepatic congestion, who were in electrolyte imbalance and died because of intensification of the diuresis effect. Deafness, tinnitus, and vertigo with a sense of fullness in the ears have occurred, most frequently in patients with severe impairment of renal function. These symptoms have been associated most often with intravenous administration and with doses in excess of those recommended. The deafness has usually been reversible in about 7 to 10 days and of short duration (one to 24 hours). However, in some patients the hearing loss has been permanent. In such cases patients were also receiving drugs known to be ototoxic. Ethacrynic acid may increase the ototoxic potential of other drugs (see PRECAUTIONS, Drug Interactions).

WARNINGS
The effects of ethacrynic acid on electrolytes are related to its renal pharmacologic activity and are dose dependent. For example, pronounced electrolyte and water loss may be avoided by weighing the patient throughout the treatment period, and administering small doses, and by using the drug on an intermittent schedule when possible. When excessive loss of sodium and chloride occurs, the drug should be withdrawn until homeostasis is restored. When excessive electrolyte loss occurs, the dosage should be reduced or the drug temporarily withdrawn.

Initiation of diuretic therapy with ethacrynic acid in the cirrhotic patient with ascites is usually accompanied by a substantial increase in urinary excretion of sodium.

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WARNINGS
General
Weakness, muscle cramps, paresthesias, thirst, anorexia, and signs of hypotension, hypokalemia, and/or hyperchloremic alkalosis may occur following oral or intravenous dosage. When ethacrynic acid is effective, alkalinization of salt intake and supplementary potassium chloride and/or aldactone are necessary. When a metabolic alkalosis may be anticipated, e.g., in cirrhosis with ascites, the use of potassium chloride or a potassium-sparing agent before and during therapy with ethacrynic acid may mitigate or prevent the hypokalemia. Loop diuretics have been shown to increase the urinary excretion of potassium, and this may result in hypokalemia. The safety and efficacy of ethacrynic acid in hypertension have not been established above the dosage of 10 mg/kg/day. When the dosage is increased, the potential for serious adverse reactions in patients from ethacrynic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ethacrynic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
There are no well-controlled clinical trials in pediatric patients. The information on oral dosing in pediatric patients, other than infants, is supported by evidence from empiric use in this age group. For information on oral use in pediatric patients, other than infants, see DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS
Gastrointestinal
Anorexia, nausea, abdominal discomfort or pain, dysphagia, nausea, vomiting, and diarrhea have occurred. These are more frequent with large doses or after one to three days of continuous therapy. A few patients have had sudden onset of profuse, watery diarrhea. Discontinue ethacrynic acid and replace lost fluids. There may be little or no effect on mortality or postural development. Functional and morphologic abnormalities were not observed. There are, however, no adequate and well-controlled studies in pregnant women.

Contraindications
Ethacrynic acid should be used during pregnancy only if clearly needed.

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Oral Use

Potassium excretion is determined in large part by the degree of fluid accumulation present in the patient. Similarly, the extent of fluid accumulation and natriuresis is largely dependent on the magnitude of diuresis or necessary. Dosage must be regulated carefully to prevent a more rapid or substantial loss of basal weight. This drug may potentiate the action of carbonic anhydrase inhibitors, with augmentation of natriuresis and kaliuresis. Therefore, when adding ethacrynic acid the initial dose and changes of dose should be in 25 mg increments, to avoid electrolyte depletion. Rarely, patients who failed to respond to ethacrynic acid have responded to older established agents. While many patients do not require supplemental potassium, the use of potassium chloride or potassium-sparing agents, or both, during treatment with ethacrynic acid is advisable, especially in cirrhotic or nephrotic patients and in patients receiving digitals.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma, and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment.

In the mouse, the oral LD₅₀ of ethacrynic acid is 627 mg/kg and the intravenous LD₅₀ of ethacrynate sodium is 175 mg/kg.

Dosage and Administration

DOSAGE

The usual intravenous dose for the average sized adult is 50 mg, or 0.5 to 1.0 mg per kg of body weight. Usually only one dose has been necessary; occasionally a second dose at a new injection site, to avoid possible thrombophlebitis, may be required. A single intravenous dose not exceeding 100 mg has been used in critical situations.

Insufficient pediatric experience precludes recommendation for this age group. To reconstitute the dry material, add 50 mL of 5% Dextrose Injection, or Sodium Chloride Injection to the vial. Occasionally, some 5% Dextrose Injection solutions may have a low pH (below 5). The resulting solution with such a diluent may be hazy or opalescent. Intravenous use of such a solution is not recommended. Inspect the vial containing intravenous ethacrynate sodium for particulate matter and discoloration before use. The solution may be given slowly through the tubing of a running infusion or by direct intravenous injection over a period of several minutes. Do not mix this solution with whole blood or its derivatives. Discard unused reconstituted solution after 24 hours. Ethacrynate sodium should not be given subcutaneously or intramuscularly because of local pain and irritation.

HOW SUPPLIED

Tablets: Ethacrynate acid, 25 mg, are white, capsule-shaped, scored tablets, coded VRX 205 on one side and EDECRIN on the other. They are supplied as follows: NDC 68682-011-10 in bottles of 100.

Intravenous Ethacrynate sodium is a dry white material either in a plug form or as a powder. It is supplied in vials containing ethacrynate sodium equivalent to 50 mg of ethacrynic acid, NDC 68682-012-27.

Storage

Store in a tightly closed container at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Tablets Ethacrynate Acid

Manufactured for:

Oceanside Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA

By:

Valeant Pharmaceuticals International, Inc.

Steinbach, MB R5G 1Z7 Canada

Intravenous Ethacrynate sodium

Manufactured for:

Oceanside Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA

By:

Patheon Manufacturing Services LLC

Burlington, VT 05408 USA

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