Australian Product Information – EDECRIN (etacrynic acid) tablets

1 NAME OF THE MEDICINE

Etacrynic acid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EDECRIN tablet contains 25 mg etacrynic acid.

Excipient with known effect: lactose monohydrate.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

EDECRIN 25 mg tablets are white capsule-shaped tablets, scored and engraved “VRX 205” on one side and the other side engraved “EDECRIN”.

The splitting of EDECRIN 25 mg tablets is not advised.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EDECRIN is indicated for the treatment of oedema when urgent diuresis by a potent saluretic-diuretic agent with rapid onset of action is essential.

- Congestive heart failure
- Pulmonary oedema
- Renal oedema
- Hepatic cirrhosis with ascites
- Oedema due to other causes

Paediatric Indications

EDECRIN tablets have been found useful in patients of the paediatric age group with the nephrotic syndrome. This experience has generally been limited to short term therapy in hospitalised patients resistant to other therapy. Paediatric patients with congenital heart disease also have responded to EDECRIN. EDECRIN should not be given to infants under two years of age. (see also section 4.3 CONTRAINDICATIONS)

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage must be carefully regulated so as to adjust the diuretic response to the rate and extent most desirable for the individual patient. Daily weighings and, when possible, serum electrolyte determinations will contribute greatly to the success of treatment.

Oral Use

The splitting of EDECRIN 25 mg tablets is not advised.

Initial Dosage

The smallest dose required to produce a gradual weight loss (about 1/2 to 1 kg per day) is recommended.

ADULTS

The recommended dose is 50 mg (2 tablets) daily immediately after breakfast. If necessary, increase the total daily dosage by amounts of 25 to 50 mg (1 to 2 tablets). The usual effective daily dosage is in the range of 50 to 150 mg (2 to 6 tablets).

Whenever a daily dosage higher than 50 mg (2 tablets) is required for desired diuresis, it should always be achieved gradually and should be divided into two doses and given after meals. In no case should a daily dosage exceed 400 mg (16 tablets).

CHILDREN

The recommended dose is 25 mg (1 tablet) immediately after breakfast. If necessary, this dosage should be carefully increased by amounts of 25 mg (1 tablet) per day until an effective diuresis is achieved. EDECRIN should not be given to infants under two years of age.

Maintenance Dosage

Treatment may be maintained either on a continuous or an intermittent basis. Intermittent therapy usually can be used without loss of therapeutic response.

The effective dosage of EDECRIN may be given on alternate days or for two- or three-day treatment periods alternating with two- or three-day rest periods.

During treatment with EDECRIN, use of supplemental potassium or potassium sparing agents is often advisable, especially in cirrhotic or nephrotic patients and in patients receiving digitalis.

Salt liberalisation usually prevents the development of hyponatraemia and hypochloraemia. During treatment with EDECRIN, salt intake may be liberalised to a greater extent than with other diuretics. Cirrhotic patients, however, usually require at least moderate salt restriction concomitant with diuretic therapy.

4.3 CONTRAINDICATIONS

- Anuria
- Oral EDECRIN is contraindicated in infants
- Hypersensitivity to any component of this product

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The effects of EDECRIN on electrolytes are related to its renal pharmacologic activity and usually are dose related. If excessive diuresis 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.

The possibility of profound electrolyte and water loss may be avoided by weighing the patient throughout the treatment period, by careful adjustment of dosage, by initiating treatment with small doses, and by using EDECRIN on an intermittent schedule when possible.

Frequent serum electrolyte, CO2 and BUN determinations should be performed early in therapy and periodically thereafter during active diuresis. Any electrolyte abnormalities should be corrected or the drug temporarily withdrawn. If increasing electrolyte imbalance, azotaemia and/or oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

EDECRIN should be given with caution to patients with advanced cirrhosis of the liver, particularly those with a history of episodes of electrolyte imbalance or hepatic encephalopathy. Like other diuretics, it may precipitate hepatic coma and death.

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 EDECRIN may mitigate or prevent the hypokalaemia.

Loop diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesaemia.

Weakness, muscle cramps, paraesthesiae, thirst, anorexia and signs of hyponatraemia, hypokalaemia and/or hypochloraemic alkalosis may occur following vigorous or excessive diuresis and may be accentuated by rigid salt restriction. Rarely, tetany has been reported following vigorous diuresis. During therapy with EDECRIN, liberalisation of salt intake and supplementary potassium chloride are often necessary.

EDECRIN should be used with caution in critically ill patients, particularly those in the following two categories:

1. Patients with severe myocardial disease who have been receiving digitalis, who may develop acute hypokalaemia with fatal arrhythmia;
2. Patients with severely decompensated hepatic cirrhosis with ascites, with or without accompanying encephalopathy, who are in electrolyte imbalance which may become aggravated. A number of possible drug related deaths have occurred among such patients.

Deafness, tinnitus and vertigo with a sense of fullness in ears have occurred in patients treated with etacrynic acid, most frequently in patients with severe impairment of renal function. A number of these patients were also receiving drugs known to be ototoxic. EDECRIN may increase the ototoxic potential of other drugs (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Antihypertensive Agents

Orthostatic hypotension may occur in patients receiving antihypertensive agents when given etacrynic acid.

Antibiotics

EDECRIN may increase the ototoxic potential of other drugs such as aminoglycoside antibiotics and some cephalosporins. Their concurrent use should be avoided.

Warfarin

A number of drugs, including etacrynic acid, have been shown to displace warfarin from plasma protein; a reduction in the usual anticoagulant dosage may be required in patients receiving both drugs.

Lithium

Lithium should generally not be given to patients receiving diuretics, since the risk of lithium toxicity is high in such patients (see package circulars for lithium preparations before such concomitant therapy.)

Corticosteroids

EDECRIN may increase the risk of gastric haemorrhage associated with corticosteroid treatment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category C

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

EDECRIN is not recommended for use in pregnancy.

Use in lactation

EDECRIN should not be given to nursing mothers. If use of the drug is deemed essential, the patient should stop nursing.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal

Anorexia, malaise, abdominal discomfort or pain, dysphagia, nausea, vomiting and diarrhoea. In a few patients watery profuse diarrhoea, gastrointestinal bleeding, and acute pancreatitis has been reported.

Metabolic

Reversible hyperuricaemia, decreased urinary urate excretion, and hyperglycaemia have been reported. Acute gout may be precipitated. Rarely, acute symptomatic hypoglycaemia with convulsions, jaundice and abnormal tests of hepatocellular function have been reported.

Haematologic

Agranulocytosis, severe neutropenia, thrombocytopenia and Henoch Schonlein purpura have been reported rarely.

Special Senses

Deafness, tinnitus and vertigo with a sense of fullness in the ears, and blurred vision have occurred.

Central Nervous System

Fatigue, apprehension and confusion.

Other

Skin rash, headache, fever, chills and haematuria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis.

In the event of overdosage, symptomatic and supportive measures should be employed. Dehydration, electrolyte imbalance, hepatic coma and hypotension should be corrected by established procedures. If required, give oxygen or artificial respiration for respiratory impairment.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

EDECRIN is a potent saluretic-diuretic agent with rapid onset of action. When administered as directed, it has been used successfully in the management of oedema of cardiac, pulmonary, renal, or hepatic origin, even oedema refractory or unresponsive to other diuretic agents.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

In both animals and man, etacrynic acid causes a marked increase in excretion of salt and water under conditions of hydropenia as well as hydration. Experimental studies indicate that etacrynic acid influences both the diluting and concentrating mechanisms of the kidney. By inhibiting active sodium reabsorption in the ascending limb of the loop of Henle, as well as elsewhere in the nephron, it depresses reversibly the operation of the diluting mechanism and diminishes the increasing solute gradient of the kidney from the cortex to the medulla. The concentrating mechanism of the more distal nephron, which is dependent on this osmotic gradient from lumen to medullary interstitium is likewise diminished. The net effect is the excretion of large amounts of virtually iso-osmotic urine. This renal effect is very different from that of the thiazides, mercurials, or other diuretics, and reflects a unique mechanism of action of etacrynic acid.

In dogs, etacrynic acid produces a maximal sodium excretion that is considerably greater than that which can be achieved with the thiazides. For example, moderate doses of etacrynic acid given intravenously (as a solution of the sodium salt) regularly caused the excretion of sodium in excess of 1000 microequivalents/minute, whereas hydrochlorothiazide even in maximally effective doses seldom caused the excretion of 500 microequivalents/minute of sodium when the animals received no prior salt supplementation. Etacrynic acid induced a chloruresis at least equal to the natriuresis in magnitude. This is in contrast to the thiazides which, especially in high doses, tend to cause increased excretion of bicarbonate as well as chloride along with sodium. Of particular interest is the fact that, with intravenous doses of etacrynic acid (as a solution of the sodium salt) sufficient to induce a maximal rate of sodium excretion several fold that evoked by a maximal dose of hydrochlorothiazide, the kaliuretic response to the two agents was

equivalent. Oral administration of etacrynic acid to dogs also caused greater saluresis than the maximum obtainable with hydrochlorothiazide.

In both acidotic and alkalotic dogs, the intravenous injection of etacrynic acid (as a solution of the sodium salt) caused an equally large excretion of sodium and of chloride. Potassium excretion also was increased to a lesser extent. Glomerular filtration rate was slightly depressed, reflecting the hypovolaemia secondary to the marked diuresis.

Following the addition of etacrynic acid (as a solution of the sodium salt) to an infusion of the maximally effective dose of hydrochlorothiazide given to dogs, the excretion of sodium, chloride, and urine increased greatly. Potassium excretion also increased, but less than proportionately. The diuretic and saluretic effects of moderate doses of etacrynic acid and hydrochlorothiazide were studied separately and together by the oral route in normal humans and in dogs. The joint effect, especially on sodium excretion, was greater than predicted from the separate effects. Etacrynic acid apparently can block an aspect of sodium reabsorption that is not affected by the thiazides.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

EDECRIN 25 mg tablets contain lactose monohydrate, maize starch, colloidal anhydrous silica, purified talc and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The tablets are packed in high density polyethylene (HDPE) bottle with a child resistant cap.

Supplied in bottles of 100.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

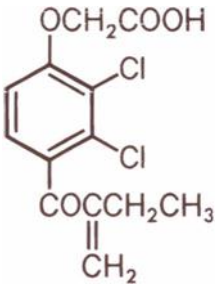
6.7 PHYSICOCHEMICAL PROPERTIES

Etacrynic 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.

Etacrynic acid is an unsaturated 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.

Its empirical formula is $C_{13}H_{12}Cl_2O_4$.

Chemical structure



CAS number

58-54-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 May 2004

10 DATE OF REVISION

12 December 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Conversion into the TGA new form for providing Product Information. Updated medicine ingredient name and minor editorial changes.

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