CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 16092/S037

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 19 1999

NDA 16-092/S-037
NDA 16-093/S-038

Merck & Co., Inc.
Attention: Larry P. Bell, M.D.
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. Bell:

Please refer to your supplemental new drug applications dated February 18, 1998, received February 19, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edecrin (Ethacrynic Acid) Tablets, and Sodium Edecrin (Ethacrynate Sodium) Injection.

We acknowledge receipt of your submissions dated August 4, 1999. Your submissions of August 4, 1999 constituted a complete response to our April 8, 1998 action letter.

These supplemental new drug applications provide for labeling revised by the addition of a storage statement to the **HOW SUPPLIED** section of the package insert and to the carton and container labels.

Additionally, we note the replacement of the
statement with the "Rx only" symbol, in accordance with section 126 of the FDA Modernization Act of 1997. We also note several, minor, editorial changes to the package insert and carton and container labels.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package inserts and immediate container and carton labels included in your August 4, 1999 submissions). Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Colleen LoCicero
Regulatory Health Project Coordinator
(301) 594-5334

Sincerely yours,

/S/ 10/19/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 16092/S037

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 16-092/S-037
16-093/S-038

Food and Drug Administration
Rockville MD 20857

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
P.Q. Box 4, BLA-20
West Point, PA 19486

APR 8 1998

Dear Dr. Bell:

Please refer to your February 18, 1998 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edecrin (ethacrynic acid) Tablets (NDA 16-092) and Edecrin I.V. (ethacrynate sodium) Injection (NDA 16-093).

The supplemental applications provide for draft labeling and labels revised by adding a storage statement to the **HOW SUPPLIED** section and to the box and container labels.

We have completed the review of these applications as submitted with draft labeling and they are approvable. Before the applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for these drugs. The labeling should be identical in content to the draft labeling and labels included in your February 18, 1998 submissions.

To each application, please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the applications.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

/S/ 4/5/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 16092/S037

FINAL PRINTED LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

TABLETS

EDECRIN®

(ETHACRYNIC ACID)

and

INTRAVENOUS

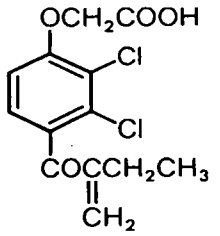
SODIUM EDECRIN®

(ETHACRYNATE SODIUM)

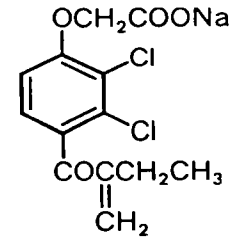
EDECRIN® (Ethacrynic Acid) is a potent diuretic which, if given in excessive amounts, may lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule must be adjusted to the individual patient's needs (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

Ethacrynic acid is an 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. 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 $C_{13}H_{12}Cl_2O_4$ and its structural formula is:



Ethacrynate sodium, the sodium salt of ethacrynic acid, is soluble in water at 25°C to the extent of about 7 percent. Solutions of the sodium salt are relatively stable at about pH 7 at room temperature for short periods, but as the pH or temperature increases the solutions are less stable. The molecular weight of ethacrynate sodium is 325.12. Its empirical formula is $C_{13}H_{11}Cl_2NaO_4$ and its structural formula is:



EDECRIN is supplied as 25 mg and 50 mg tablets for oral use. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, starch and talc. The 50 mg tablet also contains D&C Yellow 10, FD&C Blue 1 and FD&C Yellow 6. Intravenous SODIUM EDECRIN® (Ethacrynate Sodium) is a sterile freeze-dried powder and is supplied in a vial containing:

Ethacrynate sodium equivalent to ethacrynic acid	50.0 mg
Inactive ingredients:	
Mannitol	62.5 mg

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

EDECRIN 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 EDECRIN inhibits reabsorption of a much greater proportion of filtered sodium than most other diuretic agents. Therefore, EDECRIN is effective in many patients who have significant degrees of renal insufficiency (see WARNINGS concerning deafness). EDECRIN has 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 electrolyte excretion pattern of ethacrynic acid varies from that of the thiazides and mercurial 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. EDECRIN is effective whether or not there is clinical acidosis or alkalosis.

Although EDECRIN, 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 EDECRIN or within 5 minutes after an intravenous injection of SODIUM EDECRIN. 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

EDECRIN 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 due to malignancy, idiopathic edema, and lymphedema.
3. Short-term management of hospitalized pediatric patients, other than infants, with congenital heart disease or the nephrotic syndrome.
4. Intravenous SODIUM EDECRIN is indicated when a rapid onset of diuresis is desired, e.g., in acute pulmonary edema, or when gastrointestinal absorption is impaired or oral medication is not practicable.

CONTRAINDICATIONS

All diuretics, including ethacrynic acid, are contraindicated in anuria. If increasing electrolyte imbalance, azotemia, and/or oliguria occur during treatment of severe, progressive renal disease, the diuretic should be discontinued.

In a few patients this diuretic has produced severe, watery diarrhea. If this occurs, it should be discontinued and not used again.

Until further experience in infants is accumulated, therapy with oral and parenteral EDECRIN is contraindicated.

Hypersensitivity to any component of this product.

WARNINGS

The effects of EDECRIN on electrolytes are related to its renal pharmacologic activity and are dose dependent. 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 the drug on an intermittent schedule when possible. When 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.

Initiation of diuretic therapy with EDECRIN in the cirrhotic patient with ascites is best carried out in the hospital. When maintenance therapy has been established, the individual can be satisfactorily followed as an outpatient.

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

Too vigorous a diuresis, as evidenced by rapid and excessive weight loss, may induce an acute hypotensive episode. In elderly cardiac patients, rapid contraction of plasma volume and the resultant hemoconcentration should be avoided to prevent the development of thromboembolic episodes, such as cerebral vascular thromboses and pulmonary emboli which may be fatal. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium-depleting steroids.

A number of possibly drug-related deaths have occurred in critically ill patients refractory to other diuretics. These generally have fallen into two categories: (1) patients with severe myocardial disease who have been receiving digitalis and presumably developed acute hypokalemia with fatal arrhythmia; (2) patients with severely decompensated hepatic cirrhosis with ascites, with or without accompanying encephalopathy, who were in electrolyte imbalance and died because of intensification of the electrolyte defect.

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 and of short duration (one to 24

hours). However, in some patients the hearing loss has been permanent. A number of these patients were also receiving drugs known to be ototoxic. EDECRIN may increase the ototoxic potential of other drugs (see PRECAUTIONS, subsection *Drug Interactions*).

Lithium generally should not be given with diuretics (see PRECAUTIONS, subsection *Drug Interactions*).

PRECAUTIONS

General

Weakness, muscle cramps, paresthesias, thirst, anorexia, and signs of hyponatremia, hypokalemia, and/or hypochloremic alkalosis may occur following vigorous or excessive diuresis and these may be accentuated by rigid salt restriction. Rarely tetany has been reported following vigorous diuresis. *During therapy with ethacrynic acid, liberalization of salt intake and supplementary potassium chloride are often 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 EDECRIN may mitigate or prevent the hypokalemia.

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

The safety and efficacy of ethacrynic acid in hypertension have not been established. However, the dosage of coadministered antihypertensive agents may require adjustment.

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

EDECRIN has little or no effect on glomerular filtration or on renal blood flow, except following pronounced reductions in plasma volume when associated with rapid diuresis. A transient increase in serum urea nitrogen may occur. Usually, this is readily reversible when the drug is discontinued.

As with other diuretics used in the treatment of renal edema, hypoproteinemia may reduce responsiveness to ethacrynic acid and the use of salt-poor albumin should be considered.

A number of drugs, including ethacrynic 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.

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

Laboratory Tests

Frequent serum electrolyte, CO_2 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.

Increases in blood glucose and alterations in glucose tolerance tests have been observed in patients receiving EDECRIN.

Drug Interactions

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

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

A number of drugs, including ethacrynic 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.

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when EDECRIN and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect in a 79-week oral chronic toxicity study in rats at doses up to 45 times the human dose.

Ethacrynic acid had no effect on fertility in a two-litter study in rats or a two-generation study in mice at 10 times the human dose.

Pregnancy

Pregnancy Category B: Reproduction studies in the mouse and rabbit at doses up to 50 times the human dose showed no evidence of external abnormalities of the fetus due to EDECRIN.

In a two-litter study in the dog and rat, oral doses of 5 or 20 mg/kg/day (2½ or 10 times the human dose), respectively, did not interfere with pregnancy or with growth and development of the pups. Although there was reduction in the mean body weights of the fetuses in a teratogenic study in the rat at a dose level of 100 mg/kg (50 times the human dose), there was no effect on mortality or postnatal development. Functional and morphologic abnormalities were not observed.

There are, however, no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, EDECRIN should be used during pregnancy only if clearly needed.

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 EDECRIN, 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.

TABLETS
EDECRIN®
(ETHACRYNIC ACID) and
INTRAVENOUS
SODIUM EDECRIN®
(ETHACRYNATE SODIUM)
Circular Number 7901428

TABLETS
EDECRIN®
(ETHACRYNIC ACID) and
INTRAVENOUS
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7901428

TABLETS
EDECRIN®
(ETHACRYNIC ACID) and
INTRAVENOUS
SODIUM EDECRIN®
(ETHACRYNATE SODIUM)
7901428

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 INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

Safety and effectiveness of oral and parenteral use in infants have not been established (see CONTRAINDICATIONS).

Safety and effectiveness of intravenous use in pediatric patients have not been established (see DOSAGE AND ADMINISTRATION, *Intravenous Use*).

ADVERSE REACTIONS

Gastrointestinal

Anorexia, malaise, abdominal discomfort or pain, dysphagia, nausea, vomiting, and diarrhea have occurred. These are more frequent with large doses or after one to three months of continuous therapy. A few patients have had sudden onset of profuse, watery diarrhea. Discontinue EDECRIN if diarrhea is severe and do not give it again. Gastrointestinal bleeding has occurred in some patients. Rarely, acute pancreatitis has been reported.

Metabolic

Reversible hyperuricemia and acute gout have been reported. Acute symptomatic hypoglycemia with convulsions occurred in two uremic patients who received doses above those recommended. Hyperglycemia has been reported. Rarely, jaundice and abnormal liver function tests have been reported in seriously ill patients receiving multiple drug therapy, including EDECRIN.

Hematologic

Agranulocytosis or severe neutropenia has been reported in a few critically ill patients also receiving agents known to produce this effect. Thrombocytopenia has been reported rarely. Henoch-Schönlein purpura has been reported rarely in patients with rheumatic heart disease receiving multiple drug therapy, including EDECRIN.

Special Senses (See WARNINGS)

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

Central Nervous System

Headache, fatigue, apprehension, confusion.

Miscellaneous

Skin rash, fever, chills, hematuria.

SODIUM EDECRIN occasionally has caused local irritation and pain after intravenous use.

OVERDOSAGE

Overdosage may lead to excessive diuresis with electrolyte depletion and dehydration.

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 LD_{50} of ethacrynic acid is 627 mg/kg and the intravenous LD_{50} of ethacrynate sodium is 175 mg/kg.

DOSAGE AND ADMINISTRATION

Dosage must be regulated carefully to prevent a more rapid or substantial loss of fluid or electrolyte than is indicated or necessary. The magnitude of diuresis and natriuresis is largely dependent on the degree of fluid accumulation present in the patient. Similarly, the extent of potassium excretion is determined in large measure by the presence and magnitude of aldosteronism.

Oral Use

EDECRIN is available for oral use as 25 mg and 50 mg tablets.

Dosage: To Initiate Diuresis

In Adults: The smallest dose required to produce gradual weight loss (about 1 to 2 pounds per day) is recommended. Onset of diuresis usually occurs at 50 to 100 mg for adults. After diuresis has been achieved, the minimally effective dose (usually from 50 to 200 mg daily) may be given on a continuous or intermittent dosage schedule. Dosage adjustments are usually in 25 to 50 mg increments to avoid derangement of water and electrolyte excretion.

The patient should be weighed under standard conditions before and during the institution of diuretic therapy with this compound. Small alterations in dose should effectively prevent a massive diuretic response. The following schedule may be helpful in determining the smallest effective dose.

Day 1 — 50 mg (single dose) after a meal
Day 2 — 50 mg twice daily after meals, if necessary
Day 3 — 100 mg in the morning and 50 to 100 mg following the afternoon or evening meal, depending upon response to the morning dose.

A few patients may require initial and maintenance doses as high as 200 mg twice daily. These higher doses, which should be achieved gradually, are most often required in patients with severe, refractory edema.

In Pediatric Patients (excluding infants, see CONTRAINDICATIONS): The initial dose should be 25 mg. Careful stepwise increments in dosage of 25 mg should be made to achieve effective maintenance.

EDECRIN® (Ethacrynic Acid)
SODIUM EDECRIN® (Ethacrynate Sodium)

Maintenance Therapy

It is usually possible to reduce the dosage and frequency of administration once dry weight has been achieved.

EDECRIN (Ethacrynic Acid) may be given intermittently after an effective diuresis is obtained with the regimen outlined above. Dosage may be on an alternate daily schedule or more prolonged periods of diuretic therapy may be interspersed with rest periods. Such an intermittent dosage schedule allows time for correction of any electrolyte imbalance and may provide a more efficient diuretic response.

The chloruretic effect of this agent may give rise to retention of bicarbonate and a metabolic alkalosis. This may be corrected by giving chloride (ammonium chloride or arginine chloride). Ammonium chloride should not be given to cirrhotic patients.

EDECRIN has additive effects when used with other diuretics. For example, a patient who is on maintenance dosage of an oral diuretic may require additional intermittent diuretic therapy, such as an organomercurial, for the maintenance of basal weight. The intermittent use of EDECRIN orally may eliminate the need for injections of organomercurials. Small doses of EDECRIN may be added to existing diuretic regimens to maintain basal weight. This drug may potentiate the action of carbonic anhydrase inhibitors, with augmentation of natriuresis and kaliuresis. Therefore, when adding EDECRIN 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 EDECRIN is advisable, especially in cirrhotic or nephrotic patients and in patients receiving digitalis.

Salt liberalization usually prevents the development of hyponatremia and hypochloremia. During treatment with EDECRIN, salt may be liberalized to a greater extent than with other diuretics. Cirrhotic patients, however, usually require at least moderate salt restriction concomitant with diuretic therapy.

Intravenous Use

Intravenous SODIUM EDECRIN is for intravenous use when oral intake is impractical or in urgent conditions, such as acute pulmonary edema.

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 percent Dextrose Injection, or Sodium Chloride Injection to the vial. Occasionally, some 5 percent 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 SODIUM EDECRIN 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.

SODIUM EDECRIN should not be given subcutaneously or intramuscularly because of local pain and irritation.

HOW SUPPLIED

No. 3321 — Tablets EDECRIN, 25 mg, are white, capsule shaped, scored tablets, coded MSD 65 on one side and EDECRIN on the other. They are supplied as follows:

NDC 0006-0065-68 in bottles of 100.

No. 3322 — Tablets EDECRIN, 50 mg, are green, capsule shaped, scored tablets, coded MSD 90 on one side and EDECRIN on the other. They are supplied as follows:

NDC 0006-0090-68 in bottles of 100
(6505-00-834-0473, 50 mg bottles of 100).

No. 3620 — Intravenous SODIUM EDECRIN 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** 0006-3620-50.

Storage:

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

Dist by
MERCK & CO., INC., West Point, PA 19486, USA

Issued April 1998
Printed in USA

NDA 16-093

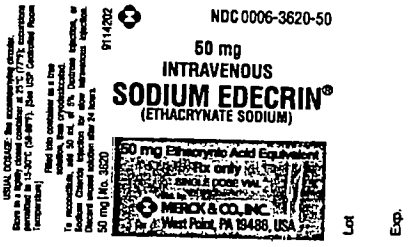
Labeling: original

NDA No. 16-093 Rc'd. 8-6-99

Reviewed by: CH 9.17.99

APPROVED

OCT 19 1999



NDA 16-093

Labeling: Original

NDA No. 16-093 Rec'd. 8-6-99

Reviewed by: CLL 9/17/99

APPROVED

OCT 19 99

50 mg Ethacrynic Acid Equivalent

(ETHACRYNATE SODIUM)

SODIUM EDECRIN®

INTRAVENOUS

50 mg | No. 3620

USUAL ADULT DOSAGE:
0.5 to 1.0 mg of ethacrynic acid per kg of body weight.
See accompanying circular.

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

50 mg | No. 3620 9234002

Minimum 30% Recycled Paperboard

Each vial contains ethacrynate sodium equivalent to 50 mg of ethacrynic acid. Inactive ingredient: 62.5 mg of mannitol.

To reconstitute, add 50 mL of 5% Dextrose Injection, or Sodium Chloride Injection for slow intravenous injection. Discard unused solution after 24 hours.

Filled into container as a true solution, then cryodesiccated.

67714

NDC 0006-3620-50

50 mg

INTRAVENOUS

SODIUM EDECRIN®

(ETHACRYNATE SODIUM)

50 mg Ethacrynic Acid Equivalent

SINGLE DOSE VIAL

Rx only

FOR THE PREPARATION OF INTRAVENOUS SOLUTIONS

Dist. by:
MERCK & CO., INC.
West Point, PA 19486, USA

N 3 0006-3620-50 5

50 mg

11

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 16092/S037

CHEMISTRY REVIEW(S)

SEP 13 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 16-093
3. Name and Address of Applicant (City & State) Merck Sharp & Dohme Research Laboratories Division of Merck, Inc. P.O. Box 4, BLA-20 West Point, PA 19486-0004		4. Supplement(s) Number(s) Date(s) S-038 2/18/98
5. Drug Name sodium edecrin IV	6. Nonproprietary Name ethacrynic sodium	8. Amendments & Other (reports, etc) - Dates amendment 8-4-99
7. Supplement Provides For: final printed labeling submitted for this amendment		
9. Pharmacological Category Diuretic	10. How Dispensed /X/ Rx /___/ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Injection	13. Potency(ies) each vial = 50 mg of ethacrynic acid	
14. Chemical Name and Structure Acetic acid, 92,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy] Sodium salt		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Draft labeling was submitted with changes made to the **"HOW SUPPLIED"** section of package insert. Storage statement was added in response to a verbal request (10/1/97) by FDA. Statement reads "Store in a tightly closed container at 25°C (77°F): excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]"

Agency's Approvable Letter (4-8-99) requested final printed labeling.

7. Conclusions and Recommendations:

Chemist portion is satisfactory.

18. REVIEWER		
Name Charlotte Brunner	Signature /S/	Date Completed 8-19-99

Distribution: ☐ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

/S/

-99

MAR 27 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 16-093
3. Name and Address of Applicant (City & State) Merck Sharp & Dohme Research Laboratories Division of Merck, Inc. P.O. Box 4, BLA-20 West Point, PA 19486-0004		4. Supplement(s) Number(s) Date(s) S-038 2/18/98
5. Drug Name sodium edecrin IV	6. Nonproprietary Name ethacrynic sodium	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: changes made to the "How Supplied" section of package insert at FDA's request.		
9. Pharmacological Category Diuretic	10. How Dispensed /X/ Rx / / OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Injection	13. Potency(ies) each vial = 50 mg of ethacrynic acid	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Draft labeling was submitted with changes made to the "**HOW SUPPLIED**" section of the package insert. Storage statement was added in response to a verbal request (10/1/97) by FDA. Statement reads "Store in a tightly closed container at 25°C (77°F): excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]"

Draft labels were also submitted with this new storage statement.

7. Conclusions and Recommendations:

Chemist portion is satisfactory.

18. REVIEWER

Name	Signature	Date Completed
Charlotte Brunner	/S/	3/27/98

Distribution: ☐ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

/S/
3.27.98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 16092/S037

ADMINISTRATIVE DOCUMENTS

OCT 19 1999

RHPC Review of Final Printed Labeling
NDA 16-092/SLR-037
[redacted]

Date of Supplements:	February 18, 1998
Date FPL submitted:	August 4, 1999
Date FPL reviewed:	September 17, 1999
Product Names:	Edecrin (Ethacrynic Acid) Tablets, 25 and 50 mg, and Sodium Edecrin (Ethacrynate Sodium) Injection, 50 mg Ethacrynic Acid Equivalent
Sponsor Name:	Merck & Co., Inc.

Evaluation:

These supplements provide for labeling revised by the addition of a storage statement to the **HOW SUPPLIED** section of the package insert and to the carton and container labels. The August 4, 1999 submissions provide for final printed labeling, as requested in the Agency's April 8, 1998 approvable letter. The approvable letter requested that the sponsor submit final printed labeling identical in content to the draft labeling and carton and container labels included in their February 18, 1998 submissions.

I reviewed the submitted package insert, and carton and container labels in their entirety. The submitted package insert and labels were identical in content to the February 18, 1998 submitted draft package insert and labels, with the following exceptions:

Container and Carton Labels

1. The "
statement has been replaced with the "Rx only" symbol on all of the immediate container and carton labels, in accordance with section 126 of the FDA Modernization Act of 1997.

The following minor, editorial changes were also noted:

Package insert

1. In the section that describes Intravenous Sodium Edecrin in the last paragraph of the **DESCRIPTION** section, the word has been changed to "ingredients".

Container and Carton Labels

1. The recycled paperboard statement on the carton label for Intravenous Sodium Edecrin (NDA 16-093) has been modified.

2. The "Dispense in a well-closed container" statement located on the container labels for both the 25 and 50 mg tablets (NDA 16-092) has been moved from the left sides of the labels to the right sides.

3. "Exp." (the abbreviation for expiration date) has been removed from the 25 and 50 mg tablet container labels (NDA 16-092).

Recommendation:

I recommend that the Division issue an approval letter for this supplement.

/S/

Colleen LoCicero, RHPC

cc: orig NDA 16-092
orig NDA 16-093
HFD-110
HFD-110/ABlount
HFD-110/LoCicero

LABELING REVIEW

APR 8 1998

NDA 16-092/S-037 Edecrin (ethacrynic acid) Tablets
16-093/S-038 Edecrin (ethacrynate sodium) Injection

Sponsor: Merck Research Laboratories
West Point, PA 19486

Date(s) of Submission: February 18, 1998

The supplemental applications provide for draft labeling and labels revised by adding a storage statement to the **HOW SUPPLIED** section of the labeling and to the label and carton labels.

The labeling was reviewed and found to be acceptable. An approvable letter will be drafted for Dr. Lipicky's signature.

/S/ 4/7/98

Gary Buehler
Project Manager

Orig NDAs
HFD-110 files
HFD-110 GBuehler
HFD-110 SBenton