CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

APPROVED DRAFT LABELING

NDC 61748-045-01

VERSAPHARM INCORPORATED

APPROVED

Aminocaproic Acid
Tablets USP 500 mg

Each tablet contains:
Aminocaproic Acid..... 500 mg

Rx only

Contents: 100 Tablets

61748045

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight container with a child-resistant closure.

Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

USUAL DOSAGE: See package insert for full prescribing information.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by: **MIKART, INC.**
Atlanta, GA 30318

Marketed by: **VersaPharm Incorporated**
Marietta, GA 30065-1509

Code 731A10

Rev. 08/00

61748045

Aminocaproic Acid Tablets USP

500 mg

℞ only

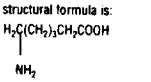
Rev. 08/00 Code 731A00

APPROVED

MAY 24 2001

DESCRIPTION:
Aminocaproic acid is 6-amino-hexanoic acid, which acts as an inhibitor of fibrinolysis.

Its structural formula is:



$C_6H_{13}NO_2$ M.W. 131.17

Aminocaproic acid is soluble in water, acid, and alkaline solutions; it is sparingly soluble in methanol and practically insoluble in chloroform.

Each Aminocaproic Acid Tablet USP for oral administration contains 500 mg of aminocaproic acid and the following inactive ingredients: magnesium stearate, povidone and stearic acid.

CLINICAL PHARMACOLOGY:
The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity.

In adults, oral absorption appears to be a zero-order process with an absorption rate of 5.2 g/hr. The mean lag time in absorption is 10 minutes. After a single oral dose of 5 g, absorption was complete (F=1). Mean ± SD peak plasma concentrations (164 ± 28 mcg/mL) were reached within 1.2 ± 0.45 hours.

After oral administration, the apparent volume of distribution was estimated to be 23.1 ± 6.6 L (mean ± SD). Correspondingly, the volume of distribution after intravenous administration has been reported to be 30.0 ± 8.2 L. After prolonged administration, aminocaproic acid has been found to distribute throughout extravascular and intravascular compartments of the body, penetrating human red blood cells as well as other tissue cells.

Renal excretion is the primary route of elimination, whether aminocaproic acid is administered orally or intravenously. Sixty-five percent of the dose is recovered in the urine as unchanged drug and 11% of the dose appears as the metabolite adipic acid. Renal clearance (116 mL/min) approximates endogenous creatinine clearance. The total body clearance is 169 mL/min. The terminal elimination half-life for aminocaproic acid is approximately 2 hours.

INDICATIONS AND USAGE:
Aminocaproic Acid Tablets USP are useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia; abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung,

hemostatic defect contributes to bleeding life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia; abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the genitourinary system). (See **WARNINGS**.)

CONTRAINDICATIONS:
Aminocaproic acid should not be used when there is evidence of an active intravascular clotting process.

When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation (DIC), this distinction must be made before administering aminocaproic acid.

The following tests can be applied to differentiate the two conditions:

•Platelet count is usually decreased in DIC but normal in primary fibrinolysis.

•Protamine paracoagulation test is positive in DIC; a precipitate forms when protamine sulphate is dropped into citrated plasma. The test is negative in the presence of primary fibrinolysis.

•The euglobulin clot lysis test is abnormal in primary fibrinolysis but normal in DIC. Aminocaproic acid must not be used in the presence of DIC without concomitant heparin.

WARNINGS:
In patients with upper urinary tract bleeding, aminocaproic acid administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. For this reason, aminocaproic acid should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk.

Subendocardial hemorrhages have been observed in dogs given intravenous infusions of 0.2 times the maximum human therapeutic dose of aminocaproic acid and in monkeys given 8 times the maximum human therapeutic dose of aminocaproic acid.

Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose and in monkeys given intravenous doses of aminocaproic acid at 6 times the maximum human therapeutic dose.

Rarely, skeletal muscle weakness with necrosis of muscle fibers has been reported following prolonged administration. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure. Muscle enzymes, especially creatine phosphokinase (CPK) are elevated. CPK levels should be monitored in patients on long-term therapy. Aminocaproic acid administration should be stopped if a rise in CPK is noted. Resolution follows discontinuation of aminocaproic acid; however, the syndrome may recur if aminocaproic acid is restarted.

The possibility of cardiac muscle damage should also be considered when skeletal myopathy occurs. One case of cardiac and hepatic lesions observed in man has been reported. The patient received 2 g of aminocaproic acid every 6 hours for a total dose of 26 g. Death was due to continued cerebrovascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

PRECAUTIONS:
General:
Aminocaproic acid inhibits both the action of plasminogen activators and, to a lesser

of renal origin unless the possible benefits outweigh the risk.

Subendocardial hemorrhages have been observed in dogs given intravenous infusions of 0.2 times the maximum human therapeutic dose of aminocaproic acid and in monkeys given 3 times the maximum human therapeutic dose of aminocaproic acid.

Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose and in monkeys given intravenous doses of aminocaproic acid at 6 times the maximum human therapeutic dose.

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PRECAUTIONS:

General:

Aminocaproic acid inhibits both the action of plasminogen activators and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis and/or laboratory finding indicative of hyperfibrinolysis (hyperplasminemia).[1]

Inhibition of fibrinolysis by aminocaproic acid may theoretically result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of intravascular clotting which followed this treatment. Rather, it appears that such intravascular clotting was most likely due to the patient's pre-existing clinical condition, e.g., the presence of DIC. It has been postulated that extravascular clots formed in vivo may not undergo spontaneous lysis as do normal clots.

Reports have appeared in the literature of an increased incidence of certain neurological deficits such as hydrocephalus, cerebral ischemia, or cerebral vasospasm associated with the use of antifibrinolytic agents in the treatment of subarachnoid hemorrhage (SAH). All of these events have also been described as part of the natural course of SAH, or as a consequence of diagnostic procedures such as angiography. Drug relatedness remains unclear.

Epsilon-aminocaproic acid should not be administered with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Laboratory Tests:

The use of aminocaproic acid should be accompanied by tests designed to determine