SUMMARY BASIS OF APPROVAL (4/12/99)
OB-NDA 20-0952

Product: OB-NDA 20-0952 - 6% Hetastarch in Lactated Electrolyte Injection (Hextend®)

Sponsor: BioTime, Inc.
935 Pardee Street
Berkeley, CA 94710

Date of Application: March 30, 1998

I. Indications for Use

Hextend® (6% Hetastarch in Lactated Electrolyte Injection) is indicated in the treatment of hypovolemia when plasma volume expansion is desired. It is not a substitute for blood or plasma.

II. Dosage Form, Route of Administration, and Recommended Dosage

Hextend® is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration as well as age, weight, and clinical condition of the patient. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required although doses of isotonic solutions containing 6% hetastarch up to 1500 mL have been used during major surgery generally without a need for blood or blood products. Volumes in excess of 1500 mL per day have been used where severe blood loss has occurred although generally only in conjunction with the administration of blood and/or blood products. Adequate well controlled clinical trials to establish the safety and effectiveness of the drug in pediatric patients have not been conducted.

III. Manufacturing and Controls

A. Chemistry

Hextend® contains high molecular weight hetastarch at a concentration of 6% as an oncotic agent to permit retention of intravascular fluid until the hetastarch is replaced by blood proteins. The hetastarch component of Hextend® is the same as in the approved Hetastarch Injection products (6% Hetastarch in 0.9% Sodium Chloride Injection). Hetastarch is an artificial colloid derived from a waxy starch composed almost entirely of amylopectin. Hydroxyethyl ether groups are introduced into the glucose units of the starch, and the resultant material is hydrolyzed to yield a product with a molecular weight suitable for use as a plasma volume expander. Hetastarch is characterized by its molar substitution and also by its molecular weight. The molar substitution is approximately 0.75 which means hetastarch has an average of approximately 75 hydroxyethyl groups for every 100 glucose units. The weight average molecular weight is approximately 670,000 with a range of 450,000 to 800,000 and with at least 80% of the polymer units falling within the range of 20,000 to 2,500,000. Hydroxyethyl groups are attached by ether linkage primarily at C-2 of the glucose unit and to a lesser extent at C-3 and C-6. The polymer resembles glycogen, and the polymerized D-glucose units are joined primarily by α-1,4 linkages with occasional α-1,6 branching linkages. The

degree of branching is approximately 1:20, which means that there is an average of approximately one α-1,6 branch for every 20 glucose monomer units.

When administered intravenously, Hextend® provides sources of water and electrolytes. Its electrolyte content resembles the principal electrolyte constituents of normal plasma.

Electrolyte	Concentration (mEq/L)
Sodium	143
Chloride	124
Lactate	28
Calcium	5
Potassium	3
Magnesium	0.9

B. Manufacturing and Controls

Hextend® is manufactured by Abbott Laboratories, North Chicago, IL 60064 (Drug Master File BB-MF2-7453) under a licensing agreement with BioTime, Inc., Berkeley, CA 94710.

C. Stability

Data indicate that the product is stable for at least two years under appropriate storage conditions. Recommended storage: Room temperature, 25 °C (77 °F).

D. Methods Validation

Abbott Laboratories has validated the analytical methods under Drug Master File [redacted]

E. Labeling

Draft labeling revised in accordance with review comments has been submitted.

F. Establishment Inspection

Hextend® is manufactured at Abbott Laboratories in North Chicago, Illinois. The most recent inspection was in April, 1997. The facility was found to be in compliance with good manufacturing practices.

G. Environmental Impact Analysis Report

N/A

IV. Pharmacology/Toxicology

A. Non-clinical Pharmacology

Hextend® has been used to exchange transfuse rats and dogs at normal body temperature. All fed rats and 80% of fasted rats that had 75-80% of their blood volume isovolemically replaced by Hextend® survived in room air without subsequent transfusions. In rats that were 70 to 80% exchange transfused, hematocrit, cholesterol, triglycerides, albumin, total protein, iron, bilirubin, and all of the enzymes that were measured were found to be decreased in concentration/activity at the end of the exchange in proportion to the degree of hemodilution. One to five days later, hematocrit had recovered to approximately 60% of normal while cholesterol and triglycerides were moderately recovered. Albumin, total protein, iron, bilirubin, and enzymes, except for alkaline phosphatase, fully recovered in concentration/activity at this time. Glucose concentration was elevated during infusion as was uric acid. However, glucose values returned to normal while uric acid continued to increase. This prolonged increase in uric acid and the persistent modest elevations in BUN and creatinine may be indicative of increased protein turnover and synthesis required to produce albumin, plasma proteins, and hemoglobin.

All dogs in which 60-70% of their blood was exchange transfused with Hextend® survived. Hematocrits and platelet counts were found to be decreased in concentration/activity at the end of the exchange in proportion to the degree of hemodilution. Three days later, hematocrits and platelet counts were only slightly recovered

B. Toxicology

1. Acute Toxicity

Acute toxicity studies in rats involved a single intravenous injection of 67, 133, or 200 mL/kg of Hextend® followed by necropsy at 7, 14, or 30 days. There were two control groups, 200 mL/kg of normal saline and 200 mL/kg of Hetastarch Injection. Paraffin-embedded, hematoxylin and eosin stained or Periodic Acid Schiff (PAS) stained tissues obtained at 7, 14, or 30 days were evaluated. Lesions were seen in the brain, heart, right and left kidneys, liver, lung, lymph nodes, adrenals, ovaries, sternum/bone marrow, testes, seminal vesicles, uterus, thymus, and spleen in most animals in all treatment groups except the saline control. The lesions consisted predominantly of activation of the mononuclear macrophage system as characterized by the accumulation of large foamy macrophages. PAS staining was slightly positive in the foamy vacuolated macrophage/mononuclear phagocytic cells consistent with glycogen accumulation (note that hetastarch resembles glycogen).

2. Subchronic Toxicity

The subchronic study carried out in dogs indicates that daily infusion of 33 mL/kg of Hextend®, approximately equal to a 50% blood volume infusion, for 14 days does appear to cause transient hematologic and clinical chemistry alterations. Activated partial thromboplastin time (APTT) was increased approximately twofold to above normal levels during the period of infusion. Factor VIII markedly decreased to 3 or 4% of pre-infusion values by day 8. However, within one day after discontinuation of infusion, the Factor VIII values reached 45% of pre-infusion values. By day 8 when APTT and prothrombin times were elevated and Factor VIII was maximally decreased, some evidence of slight bleeding was observed, for example, from gums and mouth, and subcuticular

hemorrhages were observed, usually on the legs and occasionally on the abdomen. Despite the marked changes in APTT, prothrombin time, and Factor VIII, no major bleeding was observed during the infusion period and upon necropsy.

There were no increases observed in SGOT (AST) or SGPT (ALT) in any of the animals; this suggests that the livers were not damaged by the drug.

There was evidence of grossly observable as well as histopathological changes that persisted for at least 45 days after the last dose. Lesions were seen in the adrenals, brain, ovaries, testes, heart, lungs, liver, kidneys, spleen, and lymph nodes. These changes consisted predominantly of activation of the mononuclear macrophage system as characterized by the accumulation of large foamy macrophages. PAS stain was applied to all tissues; the foamy vacuolated macrophages/ mononuclear phagocytic cells were slightly positive. Control animals given daily infusions of 33 mL/kg of Hetastarch Injection for 14 days showed quantitatively similar lesions. This is consistent with glycogen accumulation, since hetastarch resembles glycogen. The accumulation was considered reversible by the veterinary pathologists.

C. Mutagenicity Studies

No studies on mutagenicity have been performed.

D. Reproduction and Pregnancy

When intravenous daily doses of Hetastarch Injection at 2 times, 1/3 times, and 1 times the maximum recommended therapeutic human dose were administered to New Zealand rabbits, BD rats, and Swiss mice, respectively, over several days during the period of gestation, no evidence of teratogenicity was evident. There are no adequate and well controlled studies in pregnant women. Hextend® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

V. Medical

A. Pharmacokinetics

Hetastarch molecules below 50,000 molecular weight are rapidly eliminated by renal excretion. A single dose of approximately 500 mL of Hetastarch Injection (approximately 30 g) results in elimination in the urine of approximately 33% of the dose within 24 hours. This is a variable process but generally results in an intravascular hetastarch concentration of less than 10% of the total dose injected by two weeks. A study of the biliary excretion of hetastarch in 10 healthy males accounted for less than 1% of the dose over a 14 day period. The hydroxyethyl group is not cleaved by the body but remains intact and attached to glucose units when excreted. Significant quantities of glucose are not produced as hydroxyethylation prevents complete metabolism of the smaller polymers.

B. Clinical Studies

American Society of Anesthesiologists grade I, II, and III status adult patients presenting for major elective general, gynecological, orthopedic, or urological surgery with anticipated blood loss of greater than 500 mL were enrolled in randomized, controlled studies at Duke University Medical Center and The Mount Sinai Medical Center. Patients received either Hetastarch Injection or Hextend® for the treatment of hypovolemia according to a hypovolemia algorithm. Intraoperative use of albumin was prohibited.

Sixty patients were enrolled in each study. Collectively, the two treatment groups were well matched with regards to demographics, pre-existing disease, duration of anesthesia, and type of surgery. Collectively, patients in the two treatment groups received similar volumes of study drug (1596 mL Hextend® vs. 1428 mL Hetastarch Injection). Twenty one (35%) patients in the Hetastarch Injection group and 25 (42%) patients in the Hextend® group received >20 mL/kg of study solution. The percentage of patients who received blood transfusions intraoperatively and postoperatively were similar: Hextend® 35/59 (59%), Hetastarch Injection 34/58 (59%).

Baseline hemodynamic variables were similar between the two groups. There were no statistically significant differences in the changes in heart rate, blood pressure, and central venous pressure between the two groups from baseline to end of surgery. Hemodynamic goals as specified in the algorithm were achieved 63% (38/60) of the time in the Hetastarch Injection group and 65% (39/60) of the time in the Hextend® group. Postoperative hemodynamics and urine outputs were similar between the groups, and there was no difference in the postoperative administration of fluids, blood, or blood products. There were no overall differences in the laboratory measured hematological, biochemical, and coagulation variables.

There were no statistically significant differences between the two groups in the incidence of all adverse events, the incidence of or number of patients with serious adverse events, or the incidence of or number of patients with adverse events possibly related to study drugs. There was one death that occurred on day 34 in the Hextend® group that was determined not to be drug related. There were several patients in each group with coagulation-related laboratory adverse events at the end of surgery, most of whom had received more than 1500 mL of study drug and most of whom were subsequently treated with fresh frozen plasma post-surgery. These coagulation-related adverse events are most simply explained by hemodilution, and the Hextend® labeling will contain the same warning about hemodilution as the labeling for Hetastarch Injection.

The findings from this study indicate that Hextend® is as safe and effective as Hetastarch Injection when used for the treatment of hypovolemia in elective surgery.

Andrew Shrake 6-21-99

Andrew Shrake, ~~M.D.~~ Ph.D. Date
Chair, Review Committee

Mark Weinstein 6/22/99

Mark Weinstein, ~~M.D.~~ Ph D Date
Director, Division of Hematology

Martin E. Northern 6/25/99

Martin E. Northern, Regulatory Reviewer Date
Division of Blood Applications

6/25/99

FOR Mary Gustafson, Director Date
Division of Blood Applications