Summary of Basis for Approval

Reference Number: 96-1048

Drug Licensed Name: Coagulation Factor IX (Recombinant)

Manufacturer: Genetics Institute, Inc.

Drug Trade Name: BeneFIX™

I. Indication for use

BeneFIX™, Coagulation Factor IX (Recombinant), is indicated for the control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease). This indication includes the peri-operative management of hemophilia B patients undergoing surgery.

BeneFIX™ is not indicated for the treatment of other coagulation factor deficiencies (e.g., factors II, VII and X), nor for the treatment of hemophilia A patients with inhibitors to coagulation factor VIII, nor for the reversal of coumarin-induced anticoagulation. BeneFIX™ is also not indicated for the treatment of multiple liver-dependent coagulation factor deficiencies caused by liver disease or dysfunction.

II. Dosage Form, Route of Administration and Recommended Dosage

The BeneFIX™ is a sterile, non-pyrogenic, lyophilized powder for injection available in nominal dosage strengths of 1000, 500, and 250 International Units (I.U.) per vial. One International Unit is the amount of factor IX activity present in 1 ml of pooled, normal human plasma. Potency, in I.U., is determined by an in vitro one-stage clotting assay, using the World Health Organization International Standard for factor IX concentrates.

After reconstitution of the lyophilized powder with Sterile Water for Injection (USP), the 500 and 1000 I.U. dosage strengths of BeneFIX™ comprise approximately 100 I.U./ml, 0.26 M glycine, 1% sucrose, 10 mM L-histidine, and 0.005% polysorbate 80, pH 6.8. The reconstituted 250 I.U. dosage strength of BeneFIX™ comprises about one-half these concentrations or approximately 50 I.U./ml, 0.13 M glycine, 0.5% sucrose, 5 mM L-histidine, and 0.0025% polysorbate 80, pH 6.8. The 500 and 1000 I.U. dosage strengths of BeneFIX™ are approximately isotonic, whereas the 250 I.U. dosage strength is hypotonic.

The lyophilized formulation contains no preservatives, nor any added animal or human raw materials.

BeneFIX™ is administered only by intravenous infusion within 3 hours after reconstitution.

Treatment with BeneFIX™, as for all factor IX products, should be initiated under the supervision of a physician.

Clinical studies have shown that the recovery of BeneFIX™ is significantly lower (by about 28%) than that of a high purity, plasma-derived factor IX (see below). Empirically, one I.U. of BeneFIX™ per kilogram of body weight is expected to increase the circulating

activity of factor IX by 0.8 I.U./dl. The following formula provides a guide to empirical dosage calculations:

Number of factor IX I.U. required	=	Body Weight (in kg)	×	Desired factor IX Increase (%)	×	**1.2** I.U./kg

Alternatively, the estimation of the required dose of BeneFIX™ can be based on prior experience with plasma-derived factor IX and titrated upward if necessary to achieve the desired clinical response.

The proper dosage of BeneFIX™, as well as the frequency of infusion, can be expected to vary with the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of factor IX. Dosing guidelines such as given in reference 1 may be useful in estimating appropriate dosage.

For surgical interventions and for life-threatening hemorrhage, precise monitoring of the factor IX replacement therapy using a factor IX activity assay is advised.

III. Manufacturing and Controls

A. Manufacturing

The active ingredient in BeneFIX™ is Coagulation Factor IX (Recombinant), a 415-amino acid glycoprotein (approximately 55 kDa) that is produced in Chinese hamster ovary (CHO) cells. The production cells were stably transfected with the gene for the Ala^{148} allelic form of plasma-derived factor IX, which by allelic frequency would account for 20% of the factor IX in current products (the remaining 80% having Thr at this position). The production cells were also stably transfected with the gene for the human paired basic amino acid cleaving enzyme (PACE), necessary for the efficient removal of the pro-peptide from the translation product.

The post-translational modifications of the recombinant molecule have been extensively characterized and appear to be generally similar to those of the plasma-derived molecule. Subtle differences have been noted in the complexity of the N-linked carbohydrates, those found in BeneFIX™ being a subset of those occurring in the natural product. BeneFIX™ is γ-carboxylated on an average of 11.5 residues, whereas 12 residues are normally γ-carboxylated. These minor differences are not known to alter the structure or function of BeneFIX™. Of greater significance, the sulfation of Tyr^{155} (>90% in plasma derived factor IX vs. ~25% in BeneFIX™) and the phosphorylation of Ser^{158} (unphosphorylated in BeneFIX™) appear to affect the in vivo recovery of the recombinant product (see discussion of the pharmacokinetic analysis of BeneFIX™ in the clinical summary).

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1. Roberts, H.R. and Eberst, M.E. 1993. Current management of hemophilia B. Hematolol. Oncol. Clin. North Amer. 7(6): 1269-1280.

A production campaign begins by thawing an ampoule of the production cells, maintained as a Working Cell Bank, expanding the culture in spinner flasks, a bioreactor, and finally the bioreactors in which production takes place in a batch-refeed mode. As many as bioreactors may be utilized in a campaign, which may be inoculated from each other, or from the bioreactor, as validated.

The production cell line has been adapted to suspension cell culture in defined growth medium that is not supplemented by human- or animal-derived proteins. Other than the proteins secreted by the production cell line, the only protein used in the production process for recombinant factor IX is recombinant human insulin (produced in *E. coli*) which is a component of the culture medium. In addition, both the MCB and the WCB have been adapted for growth and cryopreserved (-135°C) in the absence of human or animal protein.

Recombinant factor IX is purified from the culture medium by means of a four-step chromatography process. The purification process also contains a nanofiltration step capable of reducing viral burden. Other than use of the CHO cell line and recombinant human insulin made in *E. coli*, no human or plasma products are used in the manufacture or formulation of BeneFIX™.

The drug substance is manufactured at the Andover, Massachusetts facility of Genetics Institute. Frozen (-80°C) bulk is then shipped to a contract manufacturer for final formulation, sterile filtration, aseptic filling and lyophilization. The contractor also tests the final containers for sterility and particulates, labels and packages the product and ships the released product to distribution centers. All other release testing and quality assurance functions are performed by Genetics Institute.

Final container testing includes potency, specific activity, activated factor IX, SDS-PAGE (purity and identity), SEC-HPLC (purity and protein concentration), sterility, endotoxin, appearance, moisture, solubility, pH and concentrations of the major excipients. The final drug product does not contain other proteins of any kind added as excipients or stabilizers.

B. Validation

The production cell line has been cryopreserved as a Master Cell Bank (MCB), from which a Working Cell Bank (WCB) has been derived. The MCB, the WCB, and end-of-production cells have been characterized and found to be stable in genotype and free of any detectable bacterial, mycoplasmal, fungal or viral contamination.

The manufacturing process for BeneFIX™ has been validated for consistency, robustness, and for removal of impurities. In particular, validation studies and ongoing, periodic revalidation have been accepted in lieu of lot by lot testing of drug substance or final drug product to establish the removal of certain defined

contaminants. These validation studies include removal of host cell proteins, PACE, rhInsulin, methotrexate, and DNA, and have indicated that each of these potential contaminants is reproducibly removed to acceptable levels in the final drug product.

Assays of the drug substance and the final container material have been validated for accuracy, precision and reproducibility. All final container lots have been shown to conform to requirements for identity, purity, potency and sterility according to 21 CFR Part 610. Five conformance lots have been submitted to CBER for testing and have been shown to meet the requirements for potency, residual moisture, and sterility.

Various steps in the purification process have been validated for their ability to remove viruses that may not have been detected in the production cells, above. Two of the chromatography columns and the nanofiltration step (molecular weight cutoff 70,000) were evaluated using appropriate model viruses (amphotropic murine leukemia virus, bovine parvovirus, human herpes simplex virus type I, reovirus type 3). Overall, the purification process has been show to reduce these viruses by a factor of at least 10^{10}.

Summary of Prospective Scale Evaluation of Removal/Inactivation

Virus	Q Sepharose FF	Chelate-EMD-Cu(II)	Viresolve-70	Overall
A-MuLV	6.11[a]	NA	>5.66	>11.8
BPV	5.42	2.19	4.86	12.5
HSV	4.49	3.92	>5.55	>14.0
Reo-3	5.45	0.15	5.86	11.3[b]

a Log_{10} removal value.

b Does not include the 0.15 LRV determined for the Chelate-EMD-Cu(II) column step.

C. Stability Studies

The stability of the drug substance has been investigated in four batches for up to 24 months. Data to date indicate that the drug substance is stable for 24 months when maintained at -80°C and for 6 months when maintained at -20°C.

The stability of the drug product has been investigated in three lots of the 250-I.U. dosage strength, one lot of the 500-I.U. dosage strength, and three lots of the 1000-I.U. dosage strength. Only one lot (1000 I.U.) has been studied under intended storage conditions for a full 24-month period. Data for 18 months have been accumulated for 5 other lots. Coupled with accelerated studies at room temperature and at 40°C, data to date indicate that the drug product is stable for 24 months when maintained at 2-8°C. The drug product is also stable for 6

months at room temperature. Studies of the reconstituted material have indicated that it is stable for at least 24 hours at room temperature, but nevertheless should be administered within three hours of reconstitution to assure aseptic use.

D. Labeling

The package insert and container and package labels are in compliance with 21 CFR §§ 201.57, 610.60, 610.61 and 610.62. The trademark, BeneFIX™, is not known to be in conflict with the trademark of any other biological product.

E. Establishment Inspections

A combined prelicense and biennial establishment inspection of the Andover, MA production facility of Genetics Institute was conducted from November 11 to 15, 1996 by inspectors from OELPS and OBRR, CBER and from BOS-DO. The most recent biennial establishment inspection of the McPherson, Kansas facility of Sanofi Winthrop Pharmaceuticals was conducted from August 19 to 22, 1996 by inspectors from OELPS, CBER and from KAN-DO. Both establishments were found to be in compliance with current good manufacturing practices. Copies of the inspection reports are on file.

F. Environmental Assessment

A report of the impact on the environment is included in the license application.

BeneFIX™ produces a hemostatic correction in hemophilia B dogs similar to human pdFIX as exhibited by shortened whole blood clotting time, shortened partial thromboplastin time and correction of secondary bleeding times.

Intravenous doses up to 200 I.U./kg have been administered to dogs and rats without any observed toxicity other than those associated with the development of antibodies. High doses (≥500 I.U./kg) of BeneFIX™ administered to mice by intraperitoneal injection result in thromboses and consumptive coagulopathy. By comparison with the exposure data and toxicological findings in rats and dogs, the mouse appears to be uniquely susceptible to BeneFIX™ and is therefore of uncertain value with respect to human risk assessment.

The thrombogenic potential of BeneFIX™ was evaluated in the Wessler stasis model (New Zealand White rabbits). Studies were conducted comparing BeneFIX™ with one Coagulation Factor IX Complex (Human) (PCC) and two high purity Coagulation Factor IX (Human) products (pdFIX). The PCC was administered at doses of 15 and 50 I.U./kg and as expected, thrombi were observed at both doses. BeneFIX™ was administered at doses of 50, 150, 500 and 1000 I.U./kg and each pdFIX was administered at 1000 I.U./kg. Evidence of thrombosis was seen at the high dose of pdFIX but not at the higher doses of BeneFIX™. One animal that had been treated with BeneFIX™ at 150 I.U./kg became thrombotic, but because of the lack of a dose response relationship, the latter observation was judged not to be biologically relevant.

No reproductive, developmental or carcinogenicity studies were performed. The mutagenic and clastogenic potential of BeneFIX™ was assessed by means of the Ames assay and chromosomal aberration assay with human peripheral blood lymphocytes. Both studies yielded negative results at levels of BeneFIX™ estimated to be 60-100 times greater than anticipated in the clinical population.

V. Medical

Inspections of four of the clinical sites were conducted in October 1996. The sites were found to be in compliance with current good clinical practices with regard to the Coagulation Factor IX (Recombinant) studies.

Genetics Institute, Inc. conducted four clinical studies of BeneFIX™ safety and efficacy. The first study (C9407-21) was composed of three segments. The first segment, conducted in 11 patients, was a double-masked, crossover pharmacokinetic comparison of BeneFIX™ and a high purity Coagulation Factor IX (Human) (pdFIX). After completing the first study segment, all 11 patients administered BeneFIX™ as needed for spontaneous bleeding episodes (on-demand therapy) during the second study segment. Of these patients, 10 completed the 12-month visit. A third segment, surgical prophylaxis, was included if any of the 11 patients required surgery during study participation. This study is complete.

The second study (C9408-21) is composed of three segments, the first of which is an open-label, baseline pharmacokinetic evaluation of BeneFIX™ followed by replacement therapy with BeneFIX™ as appropriate for the individual patient. The second treatment segment allows on-demand therapy identical to that of the second segment of study C9407-21 and routine secondary prophylaxis for the patients who have been on such a regimen for at least 6 months before participating in the study. As in the first study, a third segment provides for surgical prophylaxis if needed. Study C9408-21 is ongoing.

The third study (C9417-21) was a surgical prophylaxis study in which patients with factor IX deficiency were enrolled if they were to undergo elective, major surgical procedures that required factor IX replacement therapy. This study is complete.

The fourth study (C9418-21) is a study of BeneFIX™ in previously untreated patients. This study is ongoing.

A safety update was submitted November 1, 1996, reporting results accrued as of August 31, 1996. The data reported in this submission were not included in the evaluation of efficacy. One adverse event was reported to the IND subsequent to the safety update.

A. Pharmacokinetics

The crossover pharmacokinetic evaluation of BeneFIX™ and pdFIX was performed at doses of 50 I.U./kg in 11 previously treated patients. The design of this study conformed to the guidelines published by the International Society on Thrombosis and Hemostasis Both products were well tolerated and corrected the prolonged PTT characteristic of hemophilia B. Elimination half-lives for BeneFIX™ and pdFIX were not significantly different (18.1 ± 5.1 hours and 17.7 ± 5.3 hours, respectively). However, the recovery of BeneFIX™ was 28% lower than that of pdFIX (37.8 ± 14.0% and 52.6 ± 12.4%, respectively; p=0.0004). That is, BeneFIX™ produced a mean increase in circulating factor IX activity of 0.84 I.U./dl per I.U./kg administered, compared to 1.17 I.U./dl per I.U./kg for pdFIX. These pharmacokinetic parameters were similar in subsequent evaluations at 6 and 12 months. These parameters also did not differ significantly among patients treated with four drug product lots manufactured from several batches of drug substance produced from 2 separate inoculum runs.

B. Previously Treated Patients

The efficacy of BeneFIX™ in previously treated patients with moderate or severe hemophilia B was assessed in an open-label phase 1/2 and phase 2/3 study of on-demand, self-administered treatment and peri-operative use of BeneFIX™ (C9407-21 and C9408-21). The patients were not stratified according to the severity of the factor IX deficiency, nor was any attempt made to directly compare BeneFIX™ with any other product. All endpoints were based on the subjective evaluation (Excellent, Good, Moderate, No Response, Failure) by either the patient or the physician. Routine secondary prophylaxis was also subjectively graded: Excellent, Effective, Inadequate, Failure.

A total of 37 patients have been enrolled in the efficacy portions of C9407-21 and C9408-21, of whom 36 were included in the efficacy analysis. Six lots of BeneFIX™ from three separate campaigns were used in this study. No patient reported "failure" of treatment with BeneFIX™, however, one patient discontinued participation at the one month follow-up visit because of a lack of response. In 35 of 36 patients who were treated for a bleeding episode, 82% of all bleeding episodes (301/369) required a single infusion of BeneFIX™ for resolution and 5.7% (21/369) required three or more infusions. Of the infusions administered, 90% (437/488) were reported as providing excellent or good response. However, data correlating the initial dose administered with the severity of the bleeding episode were not obtained.

For patients treated on a routine secondary prophylaxis regimen 88% of responses (14/16) were rated as "excellent" or "effective" in preventing bleeding. Of 29 "spontaneous" (without concurrent injury) musculoskeletal bleeding episodes in patients on routine secondary prophylaxis, none occurred within 24 hours of an infusion and 7 occurred within 72 hours of an infusion. No data was provided regarding previous prophylactic use of pdFIX (e.g., dosing or effectiveness) or comparing the recoveries (or other pharmacokinetic parameters) of BeneFIX™ with pdFIX. The data regarding prophylactic use of BeneFIX™ is therefore considered preliminary.

Of the 36 patients enrolled in C9407-21 and C9408-21, 13 patients (on demand and prophylaxis) increased the dose of BeneFIX™ administered for subsequent bleeding episodes or ongoing prophylaxis. The results regarding the effectiveness of these dose modifications are preliminary. However, in nine surgical patients, a dose-response relationship between pre-operative bolus BeneFIX™ infusion and the first post-infusion activity was established (Pearson $r = 0.74$; $p = 0.0235$), suggesting that the lower in vivo recovery can be compensated for by a simple adjustment of the dose of BeneFIX™ administered (see page 2).

C. Surgery

As of January 19,1996, 13 procedures had been performed in 12 patients (6 enrolled in PTP studies [C9407-21 and C9408-21] and 6 exclusively enrolled in the surgical study [C9417-21]).

During the surgical period, 97% of clinical responses were rated as excellent or good by the surgeon or investigator or, when appropriate, by the patient. One patient had moderate response and no response after a single tooth dental extraction which was complicated by significant fibrinolysis. Transfusion of blood products was necessary in only 3 of the 13 procedures (orthotopic liver transplantation and two knee arthroplasties). Estimated blood loss during and after surgery was considered as expected in all cases. No bleeding episodes during the postoperative period were reported.

A total of 1,321,768 units of BeneFIX™ were used in these surgical evaluations, including baseline PK evaluations. Total dose administered per procedure during the surgical period ranged from 10,000 I.U. for a dental procedure to 348,000 I.U. for bilateral knee arthroplasties. Preoperative doses ranged from 25 to 155 I.U./kg; doses used in the postoperative period ranged from 30 to 95 I.U./kg. Continuous infusion of BeneFIX™ at a rate of 4.3 to 8.6 I.U./kg/hr was used in 3 surgeries. For the other 10 surgeries, a pulse replacement regimen was used.

D. Previously Untreated Patients

Study C9418-21 is a multicenter, open-label phase 1/2 and 2/3 safety and efficacy study of on-demand or prophylactic self-administration and peri-operative use of BeneFIX™. Nine patients had been enrolled of whom 3 had received product as of April 19, 1996. Only one patient had received product for treatment of bleeding episodes.

E. Safety

As of August 31, 1996, the clinical studies of BeneFIX™ had involved a total of 64 patients (44 previously treated patients, 11 previously untreated patients, and the 9 patients participating in the surgical study) who had received more than 7 million I.U. over a period of 18 months.

A total of 20 previously untreated patients had been enrolled, 11 of whom had been treated with BeneFIX™. No adverse reactions related to therapy have been reported after 42 infusions.

Sixty mild adverse reactions definitely, probably, or possibly-related to therapy have been reported for 2458 infusions. These were: nausea (16), discomfort at the IV site (13), altered taste (10), burning sensation in jaw and skull (6), allergic rhinitis (3), lightheadedness (2), headache (2), dizziness (1), chest tightness (1), fever (1), phlebitis/cellulitis at IV site (1), drowsiness (1), dry cough/sneeze (1), rash (1), and a single hive (1). (Data include events reported to the Blood Products Advisory Committee, December 12, 1996.)

A low-level inhibitor was detected in one of 44 patients who had an extensive (>500 exposure days) previous history of treatment with pdFIX without evidence of an inhibitor. Seroconversion in this patient was first observed in the 9-month blood sample by ELISA at 39 exposure days. This patient was able to continue treatment with BeneFIX™ with no anamnestic rise in inhibitor or anaphylaxis. By 12/96, the titer of this patient's inhibitor had decreased to undetectable levels. Samples from a second patient reacted weakly and variably in ELISA for antibody to factor IX, but the inhibitor assay remained consistently negative.

Subsequent to the filing of the safety update, Genetics Institute reported preliminary information regarding an acute renal infarct in a 31 year old male enrolled in protocol C9408-21. The patient apparently presented 12 days after the most recent infusion of BeneFIX™, at which time he was admitted to hospital. The

patient's workup was inconclusive as to the cause of the infarction, and the investigator judged that the event was unlikely to be related to the drug.

F. Post-Marketing (Phase IV) Studies

Genetics Institute has committed to continuing the following trials until completion during the post-marketing period:

C9408-21 Safety and Efficacy of Coagulation Factor IX (Recombinant) in Previously Treated Patients with Moderate or Severe Hemophilia B.

All patients currently enrolled in this study will continue in the study for a period of 2 years.

C9418-21 Study of the Safety and Efficacy of Coagulation Factor IX (Recombinant) in Previously Untreated Patients with Severe or Moderately Severe Hemophilia B

Approximately 30 patients with severe or moderately severe hemophilia B will be enrolled, at least 15 of whom will be severe hemophiliacs. All patients will be followed for at least 2 years and then up to 100 exposure days or 5 years, whichever is sooner.

VI. Blood Products Advisory Committee

On December 12, 1996, the Blood Products Advisory Committee considered the clinical data submitted in support of the license application for BeneFIX™. The committee voted eight yes, five no, with one abstention that the safety data are adequate to support the approval of BeneFIX™. In a subsequent vote, the committee voted unanimously for approval of the license application for BeneFIX™ subject to continued surveillance for: i) major thrombotic events; ii) other adverse events; iii) inhibitor development; and iv) use in previously untreated patients.

The committee also voted unanimously that the recommended dosing of BeneFIX™ be adjusted to account for the lower in vivo recovery of BeneFIX™ as compared with pdFIX.

VII. Orphan Drug Considerations

BeneFIX™ was designated an orphan drug by the Office of Orphan Products Development on October 3, 1994 (application #94-822). BeneFIX™ is the third coagulation factor IX product to receive orphan drug designation for the treatment of hemophilia B. The other two products are plasma-derived Coagulation Factors IX (Human): AlphaNine® (Alpha Therapeutic, approved December 31, 1990) and Mononine® (Centeon, then Armour Pharmaceutical, approved August 20, 1992). Currently, both plasma-derived products are manufactured by methods that are effective in reducing the risk of transmitting human viruses, however these risks have not been totally eliminated. Furthermore, the potential risk of transmitting the causative agent of

Creutzfeldt-Jakob disease (CJD) remains uncertain, but has led to the recall of large quantities of plasma derivatives.

BeneFIX™ is the recombinant analog of the two plasma derived factor IX products. It has the same principal molecular structural features as AlphaNine® and Mononine® and is intended for the same use. Hence, BeneFIX™ would be considered the same drug as AlphaNine® and Mononine® unless it can be shown to be clinically superior to the previously approved products. Genetics Institute claims the clinical superiority of BeneFIX™ because of its greater safety compared to the plasma-derived products.

By virtue of its source and manufacturing methods, BeneFIX™ is inherently less likely to transmit human blood-borne viruses and other infectious agents, and is also less likely to transmit animal-derived zoonotic agents than is AlphaNine® or Mononine®. The greater safety of BeneFIX™ with respect to its reduced risk of disease transmission is attributable to two factors:

1. BeneFIX™ is a recombinant product produced in CHO-derived cells in vitro, rather than from human plasma. Moreover, no human-derived protein is added during the production, isolation or formulation of BeneFIX™. Thus the risk of transmitting infectious agents that may be present in human plasma has been eliminated.

2. No animal derived protein is added or used during the manufacture of BeneFIX™. In particular, the affinity chromatography methods used to produce Mononine® (immobilized murine MAb) and AlphaNine® (immobilized porcine heparin), are not employed in the manufacture of BeneFIX™. Thus the risk of transmitting animal derived zoonotic agents has been reduced.

No direct comparative studies between BeneFIX™ and either AlphaNine® or Mononine® have been conducted to confirm the reduced risk of viral transmission presumed to exist for BeneFIX™. Such studies would not be practical given the small number of hemophilia B patients and the infrequency at which most blood-borne viruses are transmitted by the currently licensed products. However, it is known from epidemiological studies that human parvovirus B19 and, much less frequently, hepatitis A can be transmitted by plasma-derived coagulation factor IX preparations. These viruses do not exist in the source material from which BeneFIX™ is produced, nor in any component utilized during its manufacture. Therefore, it is reasonable to conclude that, barring a breakdown of cGMPs, the risk associated with these and other human blood-borne viruses has been eliminated in BeneFIX™.

Thus, a significant therapeutic advantage of BeneFIX™ (greater safety with respect to transmitting human viruses) over and above that provided by the approved orphan drugs, AlphaNine® and Mononine®, has been shown. In addition, BeneFIX™ is otherwise licensable and no countervailing risks have been shown to be associated with BeneFIX™. Therefore, BeneFIX™ is clinically superior within the meaning of 21 CFR 316.3(b)(3) to

either AlphaNine® or Mononine®, and may be licensed despite the orphan exclusivity of the latter two products.

VIII. Package Insert

A copy of the approved package insert is attached.

5 Feb 97
Thomas J. Lynch, Ph.D. Date
HFM-340

2/5/97
Mark J. Weinstein, Ph.D. Date
HFM-340

2/5/97
Andrew Chang, Ph.D. Date
HFM-340

2/5/97
Christine Kapfer Date
HFM-340

2/5/97
Jaroslav G. Vostal, M.D., Ph.D. Date
HFM-335

2/5/97
Laura L. Wood Date
HFM-340

2/5/97
Alicia A. Gilbert Date
HFM-207

2/5/97
Florence A. Kaltovich Date
HFM-207

Paul M. Aebersold, Ph.D. Date
HFM-380

2/10/97
Toby A. Silverman, M.D. Date
HFM-380

Jena M. Weber Date
HFM-380

Cornelius J. Lynch, Ph.D. Date
HFM-215

Jose J. Tavarez Pagan Date
HFM-650

Martin D. Green, Ph.D. Date
HFM-579