103132_5000_SBA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
103132/000

Summary Basis of Approval

Redacted documents transferred from CBER

DO NOT TAKE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUN 4 1986

Our Ref. Nos. 83-414 and 83-415

Alexander R. Giaquinto, Ph.D.
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Giaquinto:

Enclosed is Department of Health and Human Services Establishment License No. 994 issued to Schering Corporation, Kenilworth, New Jersey, with additional locations in Union, and Bloomfield, New Jersey, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture for sale, barter, or exchange those products for which your establishment holds unsuspended and unrevoked product licenses issued by the Department of Health and Human Services.

Also enclosed is a product license authorizing your establishment to manufacture and sell in interstate and foreign commerce Interferon alfa-2. Under this license you are authorized to manufacture and prepare for sale Interferon alfa-2b, recombinant, for the treatment of patients 18 years of age or older with hairy cell leukemia. In accordance with approved labeling, your product will bear the tradename, Intron A, and will be marketed as a lyophilized powder for reconstitution with Intron A diluent (bacteriostatic water for injection) in vials containing 3 million, 5 million, 10 million or 25 million IU for intramuscular or subcutaneous use.

You are requested to submit samples of each future lot of Interferon alfa-2b, recombinant, together with protocols showing results of all applicable tests. No lots shall be distributed until notification of release is received from the Director, Office of Biologics Research and Review.

The dating period for this product shall be two years from the date of manufacture when stored at 2 - 8°C in lyophilized form and one month at 2 - 8°C after reconstitution with the diluent provided. Results of ongoing stability studies should be submitted at regular intervals.

The following additional information should be submitted for review and inclusion in your product license file when available:

1. Results of ongoing clinical studies of the effects of long-term maintenance therapy on patients being treated for hairy cell leukemia.

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
BRS	Bratein	6/3	HFN-800	Cohen	6/3/86			
BRS	Zoon	6/3	HFN-885	Hamma	6-4-86			
DN								

2. Results of ongoing primate teratology and reproductive toxicology studies.

We also acknowledge receipt of your written commitment to submit adverse experience reports for Interferon alfa-2 to the Office of Biologics Research and Review in accordance with the requirements for postmarketing reporting of adverse drug experiences until such time that specific reporting requirements for biological products become effective.

Please submit three complete sets of all final printed labeling (container and package labels and package insert) and one complete package mock-up for this product along with part 2 of the label transmittal form showing implementation information. In addition, advertising and promotional labeling should be submitted for review at the time of initial publication of any advertisement and at the time of initial dissemination of promotional labeling. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claims or claims of superiority over other similar products should be made unless data to support such claims is submitted to and approved by the Office of Biologics Research and Review.

Any changes in the manufacturing, packaging or labeling of the product will require the submission of an amendment to either your product or establishment license applications for our review and written approval prior to implementation.

Information submitted under Reference Number 83-415 in support of other indications for your product will be assigned separate Reference Numbers. We will advise you, in writing, of the appropriate Reference Numbers in the near future.

Please acknowledge receipt of the enclosed licenses to the Director, Division of Product Certification, HFN-825, Office of Biologics Research and Review, Center for Drugs and Biologics.

Sincerely yours,

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

Enclosures

HFN-825:MGBEATRICE:ad 05-27-85 (0503wII)

cc: HFN-840
HFN-315
HFN-895
Mr. Beatrice
DPC

SUMMARY FOR BASIS OF APPROVAL

Reference No.:
83-415

Drug Licensed Name:
Interferon alfa-2b recombinant

Manufacturer:
Schering Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Drug Trade Name:
INTRON® A for Injection

I. Indication For Use:

INTRON® A (Interferon alfa-2b, recombinant) for injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia. Studies have shown that INTRON® A for injection can produce clinically meaningful regression or stabilization of this disease, both in previously splenectomized and non-splenectomized patients.

II. Dosage Form, Route of Administration and Recommended Dosages

INTRON® A is supplied as a lyophilized powder for reconstitution with INTRON® A diluent (bacteriostatic water for injection).

Each vial contains either 3 million, 5 million, 10 million or 25 million International Units (IU) of interferon alfa-2b, glycine, sodium phosphate dibasic, sodium phosphate monobasic and human albumin. The vials containing 10 and 25 million IU are intended for use as multidose vials.

Prior to administration, the lyophilized powder is to be reconstituted with the diluent provided, INTRON® A diluent (bacteriostic water for injection containing a compatible preservative).

Each carton will contain one vial of INTRON® A for injection and one vial of INTRON ® A diluent (bacteriostatic water for injection).

The pH of INTRON® A after reconstitution is approximately 7.2.

The recommended dosage of INTRON® A is 2 million IU/m^2 administered intramuscularly or subcutaneously three times a week. When adverse effects occur it may be necessary to withhold doses, discontinue treatment, or reduce the amount administered in each dose. The use of doses higher than 2 million IU/m^2 is not recommended.

III. Manufacturing and Controls

A. Manufacturing and Controls

Interferon alfa-2b is obtained from the bacterial fermentation of a strain of Escherichia coli bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The resultant interferon alfa-2b is a water soluble protein with a molecular weight of 19,271 daltons. The fermentation is carried out in a nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of INTRON® A is approximately 2×10^8 IU/mg protein.

A master cell bank of the genetically engineered E. coli used to produce INTRON® A has been established and is maintained by the manufacturer. This cell bank is used to produce working cell banks which are stored in aliquots. The working cell banks are tested for their suitability directly and by demonstrating their satisfactory utilization for the production of INTRON® A. The suitability of the master cell bank has been demonstrated by its satisfactory utilization for production of acceptable working cell banks.

Raw materials and packaging components used in the manufacture of INTRON® A are subjected to appropriate quality control testing.

INTRON® A is isolated from the fermentation medium using various techniques for protein purification. These techniques consist of precipitation and extraction steps, affinity and ion exchange chromatography and final crystallization.

The resulting drug substance in solution is tested for appearance and for identification by such standard methods as sodium dodecylsulfate polyacrylamide gel electrophoresis, isoelectric focusing, tryptic enzyme digest mapping and neutralization by anti-alpha interferon antibodies. It is tested for potency by an antiviral assay method, protein by the Lowry method, absence of tetracycline, purity by gel electrophoresis, DNA content and percent N-terminal methionine.

Human serum albumin produced by a U.S. licensed manufacturer is used as an excipient.

The final product is compounded, sterilized via filtration, filled into final containers and lyophilized by procedures appropriate to maintaining and preserving the purity, potency, identity and quality of the finished drug. In addition to potency and identity

testing similar to that performed on the drug substance in solution, the final product is tested for pH and moisture content, as well as for sterility, safety and endotoxin in accordance with CFR requirements for biologicals.

The potency of INTRON® A is expressed in terms of International Units (IU). International Units are determined by comparison of the antiviral activity of the INTRON® A with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organization (WHO).

The consistency of the process for manufacture of INTRON® A was demonstrated by laboratory and clinical testing of multiple lots, including more than five consecutive lots, produced for clinical trials.

INTRON® A is manufactured in compliance with current good manufacturing practices.

B. Stability Studies

Stability studies support the proposed twenty-four month expiration dating at 2°-8°C for the lyophilized product and one month at 2°-8°C after reconstitution with an appropriate preserved diluent. Stability studies are being continued.

C. Validation

System validation was performed on the processing equipment performing operations required for the manufacture and testing of the product. Equipment such as sterilizers, process air filtering, lyophilizers, water processing, cleaning procedures and analytical equipment have been validated.

D. Labeling

The labels, cartons and package insert are in compliance with applicable regulations. A package insert (Exhibit 1) will be dispensed with each package. Additionally, a patient information leaflet will be supplied in each package in order to provide adequate reconstitution and handling procedures (Exhibit 2).

E. Establishment Inspection

The facilities and procedures used for the manufacture and control of this product were inspected and are in compliance with current good manufacturing practices.

F. Environmental Impact Analysis Report

An EIAR was filed by Schering Corporation. A finding of no significant environmental impact as a result of licensing this product is attached. (Exhibit 3) A summary of the procedures taken by the manufacturer is presented below.

During fermentation, the exhaust air is discharged through sterilizing filters to the atmosphere. This does not affect the quality of the environment. Culture fluids of the fermentors are inactivated by acidification, and the entire fermentation system (including cell debris) is thermally decontaminated at the end of each batch. Liquid wastes from fermentation, isolation and purification are collected on site, neutralized and then discharged to a publicly owned sewer system.

Schering Corporation voluntarily complies with the guidelines published by the National Institutes of Health for Research involving Recombinant DNA Molecules and is also in compliance with other applicable Federal, state and local statutes and regulations regarding control of emissions.

The use of INTRON®A is not expected to have any significant effects on the environment since its component parts are naturally occurring, are subject to biological degradation and do not bioaccumulate.

The environmental assessment analysis report prepared by Schering for the manufacture and use of INTRON® A addressed the environmental impact considerations of 21 CFR, Part 25. Therefore, following review of the submitted information and inspection of the establishment it was concluded that the information provided for this environmental assessment supports the finding of no significant impact on the environment.

IV. Pharmacology:

A. Pharmacological Activities

Preclinical studies submitted to the licensing application have demonstrated the following pharmacological activities of INTRON® A: inhibition of virus replication in virus-infected cells, suppression of cell proliferation, immunomodulating activities, and interaction with specific cell membrane receptors.

INTRON® A has exhibited antiproliferative effects in preclinical studies employing both cell culture systems and human tumor xenografts in animals and has demonstrated significant immunomodulatory activity in vitro.

The antiproliferative activity of INTRON®A was evaluated in vitro using mouse and human leukemia cell lines and human osteosarcoma, melanoma and normal amnion cells. Varying amounts of antiproliferative activity of INTRON® A was observed with some human tumor cell lines. No activity was seen in mouse leukemia cells, a finding consistent with the known species-specificity of interferons.

The immunomodulating activity of INTRON® A was demonstrated in vitro by its augmentation of the spontaneous "natural killer" activity of human lymphocytes and its enhancement of the tumoricidal activity of human monocytes against human osteosarcoma cells. These effects appear to be dose dependent.

INTRON® A injected intralesionally (0.2 million or 0.8 million IU once daily for 7 days) delayed the development and reduced the volume of human osteosarcoma implants in athymic mice. The effect was dose-related. Additionally, subcutaneous administration of INTRON® A at a dose of 0.2 million units/day inhibited the growth of implanted human breast tumor xenografts in athymic mice by about 50% after 23 days.

B. Animal Toxicology

A number of preclinical studies were performed. The model systems used were selected by the manufacturer.

1. Acute Toxicity

Single doses of INTRON® A were administered to rats, mice and monkeys by both the intramuscular and intravenous routes in four separate studies. The animals were then observed for 14 days. No adverse effects were observed. The following is a list of doses used and the number and species (strains) of animals tested at these doses.

a. Doses of 1.65×10^8 units/kg (IV) and 3.3×10^8 units/kg (IM) were each administered to groups of 10 male and 10 female rats (SD).

b. Doses of 1.65×10^8 units/kg (IV) and 3.3×10^8 units/kg (IM) were each administered to groups of 5 male and 5 female rats (Fischer).

c. Doses of 1.65×10^8 units/kg (IV) and 3.3×10^8 units/kg (IM) were each administered to groups of 5 male and 5 female mice (ICR).

d. Doses of $2.6x10^8$ units/kg (IV) and $1.3x10^8$ units/kg (IM) and $2.6x10^8$ units/kg (IM) were each administered to groups of 2 male and 2 female rhesus monkeys.

e. Cardiovascular Activity

Doses of $1x10^6$ units/kg were administered intravenously to 6 male cynomolgus monkeys.

No effect on blood pressure was noted, and heart rate increased approximately 10%. There were no changes in PR or QRS intervals, but slight shortening of the QT interval was noted.

f. Behavior/Autonomic Function

Doses of $2.5x10^5$ units/kg, $5x10^5$ units/kg, and $1x10^6$ units/kg were administered intravenously. Each dose was administered to groups of 10 male mice.

No changes in behavior, neurologic function or autonomic function were noted.

2. Kidney Function

Doses of $3x10^5$ units/kg and $1x10^6$ units/kg were administered intravenously. Each dose was administered to groups of 6 male rats.

No changes in kidney function were observed.

3. Subchronic Toxicity

No major physiologic or pathologic changes were induced in rats, mice or monkeys by INTRON® A. The following is a brief description of studies performed.

a. A twenty-four day (9 consecutive daily injections) intraperitoneal study was performed in mice (BDF1 and Swiss nude). Groups received $5x10^6$ units/kg or $5x10^7$ units/kg per dose.

No adverse effects were noted.

b. One month intramuscular study was performed in rats (SD). Doses of $1.1x10^6$ units/kg were administered to 15 males and 15 females.

Occasional muscle fiber degeneration (9/30 INTRON® A, 5/30 controls) and focal myositis (6/30 INTRON® A, 3/30 controls) at injection site were noted.

c. A four week intramuscular study was performed in rats (Fischer 344) using doses of $1x10^6$ units/kg, $3x10^6$ units/kg, and $1x10^7$ units/kg. Each dose was administered to groups of 10 males and 10 females.

No toxicologic changes were noted.

d. A three month intramuscular study was performed in rats (SD). Doses of $4x10^6$ units/kg, $2x10^7$ units/kg, $1x10^8$ units/kg, were administered. Each dose was administered to groups of 10 females and 10 males.

No toxicologic changes were noted. Mild to moderate focal to diffuse nonsuppurative inflammatory lesions observed in the vicinity of the injection site of most animals. Minimal to mild myositis observed at injection sites of some control rats.

e. A one month intramuscular study was performed in cynomolgus monkeys . Doses of $1.1x10^6$ units/kg were administered to 3 males and 3 females.

Focal myositis and lymphocytic infiltration were observed at the site of injection.

f. A four week study where 7 intramuscular injections ($1x10^6$ units/kg) were given on alternate days followed by alternate days of 7 intravenous injections ($1x10^7$ units/kg). These doses were administered to 3 female rhesus monkeys.

Transient (12-24 hours) leukopenia was observed in some animals after the first IM and IV injections, no other adverse effects observed.

g. A four week intramuscular study was performed in cynomolgus monkeys. Doses of $2.5x10^5$ units/kg, $7.5x10^5$ units/kg, and $2.5x10^6$ units/kg were administered. Each dose was administered to groups of 3 females and 3 males.

Mild myositis was observed at injection sites.

h. A three month intramuscular study was performed in cynomolgus monkeys. Doses of $4x10^6$ units/kg, $2x10^7$ units/kg, and $1x10^8$ units/kg were administered. Each dose was administered to groups of 4 males and 4 females. Doses of INTRON® A up to $2x10^7$ units/kg were well tolerated. Slight decreases in red blood cell and platelet counts were observed at $1x10^8$ units/kg.

4. Teratology and Reproductive Toxicology

a. Non-Human Primates.

A reproductive toxicology study of INTRON® A in non-human primates is in progress. Another interferon alfa-2 induced menstrual cycle abnormalities and had abortifacient activity when studied in rhesus monkeys.

b. Segment II Rat (SD) (Teratology)

Doses of $1x10^5$ units/kg, $1x10^6$ units/kg, and $1x10^7$ units/kg, were administered intramuscularly for 11 days (days 7 to 17 of pregnancy). Each dose was administered to groups of either 33 or 34 gravid females. Eleven animals per group were allowed to deliver and rear pups.

No maternal toxicity was observed. Mild lethal effects on fetuses were observed at $1x10^7$ units/kg. The maximum no-effect dose was estimated to be $1x10^6$ units/kg.

c. Segment II Rabbit

Doses of $1x10^5$ units/kg, $1x10^6$ units/kg, and $1x10^7$ units/kg were each administered intramuscularly for 13 days (days 6 to 18 of pregnancy). Each dose was administered to groups of either 12 or 13 gravid females. No adverse effects in dams or fetuses were observed. The maximum no-effect dose was $1x10^7$ units/kg.

5. Mutagenicity

INTRON® A exhibited no mutagenic effects when subjected to three standard tests for mutagenicity.

a. Reversion test: Salmonella typhimurium and Escherichia coli. No mutagenic effect was noted in either the presence or absence of metabolic activation systems.

b. DNA-repair test: Bacillus subtilis [recombination repair deficient strain M45 (rec-) and wild type repair Proficient strain H17 (rec+)]. No growth inhibition was observed at any dose level with either strain of B. subtilis.

c. Mouse micronucleus assay: bone marrow erythrocytes. INTRON® A did not induce micronucleation of bone marrow erythrocytes or alter the ratio of polychromatic to normochromatic erythrocytes.

6. Pharmacokinetics in Animals

The pharmacokinetics of INTRON® A was studied after intramuscular administration to rats (Fischer) with the following results.

Tissue concentration of INTRON® A peaked at one hour and the order of concentration was kidneys > serum > lungs > liver > spleen. All tissue concentrations declined at the same rate after peaking and were less than 1/30 of the peak concentration 6 hours after dosing.

When INTRON® A was administered once daily for three weeks, concentrations in serum, lungs and spleen one hour after administration increased with repeated dosing. However, on day 21, the increases were not more than 1.7 times the concentrations one hour after the initial dose. At 24 hours after dosing on day 21, concentrations in kidneys, lungs, liver and spleen were below the limit of detectability and concentration in serum was low. After 72 hours, serum concentration was below the detectability limit.

Almost no INTRON® A was excreted in urine or bile.

No INTRON® A was observed in fetuses after administration to pregnant rats.

C. No noteworthy adverse effects were observed in the animal studies submitted to the licensing application. Due to the known species-specificity of interferons, the effects in animals were not expected to be predictive of effects in humans.

D. The package insert adequately describes the pharmacology of this product.

V. Medical.

BRIEF DESCRIPTION OF EACH STUDY

A. Pharmacokinetics

The pharmacokinetics of INTRON® A were studied in healthy male volunteers following single 10 million IU doses administered subcutaneously, intramuscularly and as a 30 minute intravenous infusion. The mean serum level concentrations of interferon following subcutaneous and intramuscular injections were comparable. The maximum serum levels obtained via these routes were approximately 150 to 180 IU/ml 6 to 8 hours after administration. The elimination half-lives of interferon following both subcutaneous and intramuscular injections were approximately 6 to 7 hours. Serum levels were below the detection limit of 25 IU/ml 24 hours after the injections. After intravenous administration, serum levels of interferon peaked (546 IU/ml) by the end of the infusion, then declined rapidly with time, becoming undetectable 4 hours after the infusion.

Following a single dose of 10 million IU of INTRON® A, interferon could not be detected in urine following any of the three routes of administration. Preliminary studies with isolated and perfused rabbit kidneys have shown that the kidney may be the main site of interferon catabolism; in addition, the kidney is important in catabolizing proteins with molecular weights below 50,000 daltons.

The pharmacokinetics of INTRON® A following intravenous and intramuscular administration of doses ranging from 1 to 100 million IU were studied in patients with various malignancies. Findings were similar to those reported for normal subjects. Intravenous administration of INTRON® A revealed a biphasic disappearance curve with an elimination half-life to 1.9 to 2.9 hours. Half-life following intramuscular administration was 0.9 to 3.1 hours. Fever, chills, myalgia and arthralgia were common after intramuscular administration; hypotension occurred only following high doses given by the intravenous route.

B. Clinical Trials in Hairy Cell Leukemia (HCL)

1. The potential for interferon in the treatment of HCL was first suggested in a small trial with partially purified leukocyte (alpha) interferon in patients relapsing from or not responding to prior therapy, primarily splenectomy. Ten of eleven patients had significant improvement in hematologic variables. Remissions occurred within two to four months and had lasted 3+ to 12+ months at the time of the initial report.

Based on the success of this trial with partially purified leukocyte interferon, a program was initiated to study treatment with subcutaneously administered INTRON® A. The intent of this treatment is to induce clinically significant improvement in the hematologic abnormalities with the potential result of lowering the incidence of infection and reducing the transfusion requirement.

2. Phase 2/3 Study

a. Study Design

An open label clinical study in 26 centers in the United States, Canada and Europe was conducted to evaluate the safety and efficacy of INTRON® A in the treatment of HCL. All centers used the same protocol. One hundred forty-five of the 163 patients enrolled were eligible for evaluation in the study based on having six months of treatment data available as of the clinical cut-off. Data for 85 evaluable patients were included with the original license application and an additional 60 patients were added in a subsequent submission.

The group was characteristic demographically of patients with HCL. It was composed of middle-aged patients, primarily men, most of whom had been splenectomized and had histories of infections or transfusions and were cytopenic at entry. The open-label study was designed to treat patients with progressive disease who had failed on standard therapies. At entry all patients required therapy for their disease, i.e., cytopenias, progressive blood or bone marrow infiltrate, increasing transfusion requirements or chronic infection.

Patients were to receive subcutaneous injections of INTRON® A three times a week. Treatment was administered on an outpatient basis unless a patient was hospitalized for another reason. For those patients deemed competent to do so, self administration was permitted.

Patients were to begin treatment at two million IU/m^2. After twelve weeks, the dose could be increased at the investigator's discretion to 5 million IU/m^2 for patients who had achieved less than a complete response. After eight more weeks, the dose could be increased to 10 million IU/m^2. Patients who failed to show any

response after eight weeks at the highest dose (28 weeks total) were to be withdrawn from the study. Responding patients could continue in the study by agreement between the investigator and the sponsor.

b. Control Data Bases

Detailed medical records were obtained for each patient for the previous six months, including all transfusion requirements, granulocyte counts, platelet counts and hemoglobin levels. All episodes of clinical infection (i.e., fever during periods of granulocytopenia or other evidence such as fever plus infiltrate on chest roentgenogram were recorded along with start and resolution dates, results of any cultures and therapy. These data served as the patients' own control for the INTRON® A treatment period.

Since HCL is a relatively rare disease where the outcome is predictable and responses are measured objectively, the sponsor compared the results of the clinical trial to an historical data base. Three investigators who participated in the clinical trials of INTRON® A therapy in HCL were asked to review their records for the past ten years and identify a cohort of HCL patients who would have been eligible for interferon therapy had the drug been available. These patients were to meet the same eligibility criteria as patients included in the open-label study with INTRON® A. Data were requested for a one-year period from the time the eligibility criteria were met. The cases provided by the investigators were reviewed by the sponsor to ensure that a valid cohort had been obtained, and seventy-one patients met the inclusion criteria.

Fifteen percent of these patients received only supportive care without chemotherapy. Of the 85% who were given chemotherapy, 72% received chlorambucil at some time during the study period.

Responses in the historical population were evaluated by changes in the values of the same three hematologic variables (granulocyte count, platelet count, hemoglobin level) followed in the open-label study. Changes in the bone marrow could not be considered because complete bone marrow data were not available for most patients.

Transfusion requirements and the incidence of infection were analyzed to determine the clinical benefit of therapy. All evaluations were done in a manner similar to that used for INTRON® A patients.

c. Response Criteria

Therapeutic response to INTRON® A was evaluated in terms of effect on seven criteria: granulocyte count, platelet count, hemoglobin level, bone marrow involvement, transfusion requirements, occurrence of severe infections and survival. Bleeding diatheses were too infrequent to permit comparisons between groups. Patients were rated as achieving objective responses which was either complete (CR), partial (PR), minor (MR), or no response (NR). A review of the specific criteria for the objective responses are presented in Table 1. Because patients could have variable disease manifestations at enrollment, a patient was not considered to have responded until there was improvement during treatment in at least one variable that was abnormal at entry without deterioration in other variables.

Safety was assessed via evaluation of adverse experiences directly observed by physicians or recorded by patients and by evaluation of changes in laboratory test results.

d. Efficacy: Patients as Their Own Controls

A summary of the results regarding efficacy follows:

- 108/145 (74%) INTRON® A-treated patients achieved a complete or partial response as of November 14, 1985. If minor responses were included, then 124/145 (86%) patients responded. One hundred twenty-two (84%) patients were treated for at least 24 weeks and 91 (63%) patients were treated for at least 36 weeks. Almost half of the patients (67 [46%]) were treated for more than 48 weeks.

- Median granulocyte, platelet and hemoglobin values increased with INTRON® A therapy. Median values were at normal levels after two to five months of treatment and continued to improve beyond six months (See Figure 1). No improvement was observed in the 6 months prior to therapy.

- The improvement in granulocyte counts correlated with reduction in frequency of severe infections.

- The proportion of patients who required platelet or red blood cell transfusions decreased during treatment with INTRON® A. The decreases paralleled the increasing values for platelet counts and hemoglobin values (See Figures 2 and 3).

- Bone marrow involvement decreased during treatment, with the maximum decrease requiring eight to ten months of treatment. It was noted that major decreases in bone marrow involvement are not necessary to effect clinically relevant improvement in hematologic variables.

- Splenectomized and nonsplenectomized patients responded alike with 16/24 (67%) non-splenectomized patients achieving objective responses (88% counting minor responses), with similar improvements in transfusion requirements indicating several of hypersplenism.

e. Efficacy: Historical Controls

A comparison was made between the original 85 patients treated with INTRON® A and the 71 patients in the historical control population as previously defined. There was little or no improvement in the historical population in hematologic variables over the one-year study period. Decreases in transfusion requirements and decreases in the incidence of infection were less pronounced than in the INTRON® A group.

Eighteen percent of the historical control patients in contrast to 73% of INTRON® A treated patients achieved a partial response.

The cumulative death rate in the historical control group was 20/71 (28%) in the one-year period, with 15/71 (21%) dying in the first six months. In contrast, the death rate for the INTRON® A group was 5% (4/85) with all deaths occurring within the first two months. The cumulative death rate from infection in the historical group was 23% over the one-year study period. In contrast, during the same period only 2% of the INTRON® A treated patients died of infection, and these occurred within the first two months.

The INTRON® A patient data base was subsequently updated to include 145 patients. Survival analyses were then performed on the following groups of patients:

- 145 INTRON® A-treated patients vs 71 historical patients;

- 121 splenectomized INTRON® A-treated patients vs 67 splenectomized historical patients;
- 121 splenectomized INTRON® A-treated patients vs 24 nonsplenectomized INTRON® A-treated patients.

Survival curves were generated via Kaplan-Meier estimates, and the curves were compared via Breslow and Mantel-Cox statistics; the Breslow test gives greater weight to early observations, whereas the Mantel-Cox test gives greater weight to later events. Observations beyond 24 months were not used in these analyses so that the follow-up times would be comparable between the groups.

Figure 4 demonstrates the superior actuarial survival achieved by the 145 INTRON® A-treated patients compared with the 71 historical control patients. The curve showing probability of survival at any time with INTRON® A therapy reaches a plateau within the first few months and remains at >90% probability of survival for the remainder of the 24-month observation period. The curve showing probability of survival with standard, historical therapy is similar to the curve for INTRON® A for the first few months, but then diverges from the INTRON® A curve. The difference between the two groups actuarial survival curves is statistically significant according to both the Breslow and Mantel-Cox tests ($P<.001$).

During the 24-month period, death was recorded for 11/145 (8%) INTRON® A-treated patients and 26/71 (37%) patients treated with standard, historical therapy.

When actuarial survival is compared between the 121 splenectomized patients who had received INTRON® A and the 67 splenectomized patients in the historical control group, the results are similar to those for all patients (Figure 5). As before, the INTRON® A curve plateaus at >90% probability of survival early in observation and continues out to 24 months (the limit of analysis), whereas the historical control curve rapidly declines thereafter. The difference between these two subgroup actuarial survival curves is statistically significant according to both the Breslow and Mantel-Cox tests ($P<.002$).

During the 24-month period, death was recorded for 9/121 (7%) INTRON® A-treated patients and 23/67 (34%) patients treated with standard, historical therapy.

Comparison of actuarial survival for the 121 splenectomized and 24 nonsplenectomized patients who received INTRON® A shows no difference (Figure 6), both curves plateau at >90% probability of survival early in therapy (at month 3). Comparison of the data via Breslow and Mantel-Cox tests shows no significant difference (P>.85).

During the 24-month period, death was recorded for 9/121 (7%) splenectomized and 2/24 (8%) nonsplenectomized patients treated with INTRON® A.

f. Safety

INTRON® A was demonstrated to be safe and well tolerated in this population of hairy cell patients as demonstrated by the following results.

- The predominant adverse experiences reported were mild (WHO grade 1) to moderate (WHO grade 2) flu-like symptoms. Severe reactions (WHO grade 3) were uncommon and most were flu-like. There was only one very severe or life threatening reaction (WHO grade 4) reported (acute renal failure associated with disseminated aspergillosis).

- Transient skin rashes of predominantly mild to moderate severity occurred intermittently in 30% of the patients. However, these did not progress in severity, and no dose modification or discontinuation was required.

- Only 5/145 (3%) patients showed or displayed CNS side-effects (WHO grade 3), somnolence, depression or confusion. There was no incidence of clinically significant cardiovascular toxicity.

- Significant laboratory abnormalities were limited to increases in hepatic enzymes, mainly SGOT and SGPT levels, 4 and 13% respectively.

- o Blood cell counts were often depressed during the first one or two months of treatment. White blood cell counts fell below 500/mm^3 in the majority of patients. Less often hemoglobin levels fell below 8 gm/dl and platelet counts fell below 50,000/mm^3.

- o Few patients (3/145) discontinued treatment because of adverse experiences, and dose adjustments were rare.

- o No interferon neutralizing factors were detected in any serum samples collected during or after treatment (N=87 Patients).

- o In this study, where the median duration of treatment was 11+ months, no cumulative toxicity was seen.

g. Summary of Clinical Trials in Hairy Cell Leukemia

Survival analyses showed a significantly higher probability ($P<.001$) of survival among INTRON® A-treated patients than among patients who received standard, historical therapies, and no difference in survival between splenectomized and nonsplenectomized patients who received INTRON® A. All deaths recorded in the INTRON® A group occurred during the first three months of therapy, which is approximately the length of time needed to obtain the optimum effect of INTRON® A treatment. However, in the group treated with standard, historical therapy, deaths occurred throughout the 12-month observation period.

C. Overall Safety of INTRON® A

In addition to the specific safety data regarding HCL trials, the manufacturer pooled the safety data from 867 patients with malignancies who have been treated systemically. These represent pooled data from six major studies reported to the OBRR. A large number of additional patients have also been treated, however, their data is not yet fully analyzed for statistical pooling purposes. The total clinical experience with INTRON® A in patients with malignancies now numbers over 1500 patients. There have been no additional unusual or unexpected side effects beyond those reported in this comprehensive review of data. The major conclusions of this analysis of toxicity follow:

- Overall, 93/867 (10.7%) patients discontinued treatment because of adverse experiences. However, in the HCL studies where most patients received doses <5 million IU, the discontinuation rate for adverse experiences was <3%.

- One patient death due to hypotension was considered by the investigator to be probably related to treatment. This patient was being treated for a malignancy other than HCL. Other patient deaths were considered possibly related to interferon treatment, but alternative causes of death were either documented or more likely.

- The most prevalent toxicities were flu-like symptoms, predominantly fatigue and fever. These were dose related. Other frequent toxicities included transient leukopenia and increases in hepatic transaminases.

- CNS toxicity occurred in 34% of patients (8% grade 3 or 4) and consisted primarily of somnolence and confusion; these effects were more prevalent in the elderly.

- Cardiovascular toxicity consisted primarily of hypotension (usually mild or moderate) and tachycardia. Evidence that INTRON® A might be associated with direct cardiotoxicity or true arrhythmogenic activity was not found. Cardiovascular disorders that were considered possibly or probably treatment-related were more prevalent in older patients.

- No clear evidence of renal toxicity was seen. Fever or dehydration resulting from treatment may be associated with azotemia.

- There was no evidence of cumulative toxicity in any major organ system, and patients developed increasing tolerance to some symptoms during long-term treatment.

CONCLUDING DISCUSSION

Hairy cell leukemia is a chronic, progressive lymphoproliferative disease. No existing medical therapy had provided consistent or sustained improvement to patients, whereas INTRON® A produced sustained responses in 74% of patients (86% including minor responses). This improvement, which is continuing, has translated into a reduction or elimination of life-threatening infections and chronic transfusion requirements.

A comparison of the patients own control data bases (six months pre-treatment observation INTRON® A treated patients vs the twelve month historical, conventionally treated patients) demonstrate that patients with progressive hairy cell leukemia do not experience spontaneous remission with high frequency. In terms of survival, INTRON® A is superior to historical treatment. Both splenectomized and non-splenectomized patients benefitted from INTRON® A therapy.

The results of these clinical trials were reviewed by the Vaccines and Related Biologic Products Advisory Committee on January 23, 1986. The Committee concurred that the data indicated effectiveness. There was some concern about safety early during treatment which was resolved by data submitted subsequently indicating improved survival.

ADEQUACY OF THE NEW DRUG LABELING

Based on the results presented in this submission, it is concluded that INTRON® A, when administered in accordance with the package insert, is safe and effective in the treatment of hairy cell leukemia. A copy of the approved package insert is attached. (Exhibit 1)

Gerald V. Quinnan, Jr., M.D.

Kathryn C. Zoon, Ph.D.

Philip D. Noguchi, M.D.

TABLE 1 - RESPONSE CRITERIA

Complete Response (CR)

Normalization of all three hematologic variables --

granulocyte count $\geq$ 1,500/mm^3
platelet count $\geq$ 100,000/mm^3
hemoglobin level $\geq$ 12 g/dl; and
no transfusion requirement; and

Fewer than 5% morphologically appearing hairy cells in the bone marrow, and

No hairy cells in the peripheral blood.

Partial Response (PR)

Normalization of all three hematologic variables as described above, and

No transfusion requirement

To indicate significant improvement in hairy cell bone marrow involvement, patients who also had $\geq$ 50% decrease from baseline (but not reaching CR) were further categorized as having a pathologic partial response (PPR). The other partial responders who fulfilled the basic requirements were categorized as having a hematologic partial response (HPR).

Minor Response (MR)

Normalization of any one hematologic variable that was abnormal at baseline, without deterioration in another variable.

No Response (NR)

Anything less than a minor response.

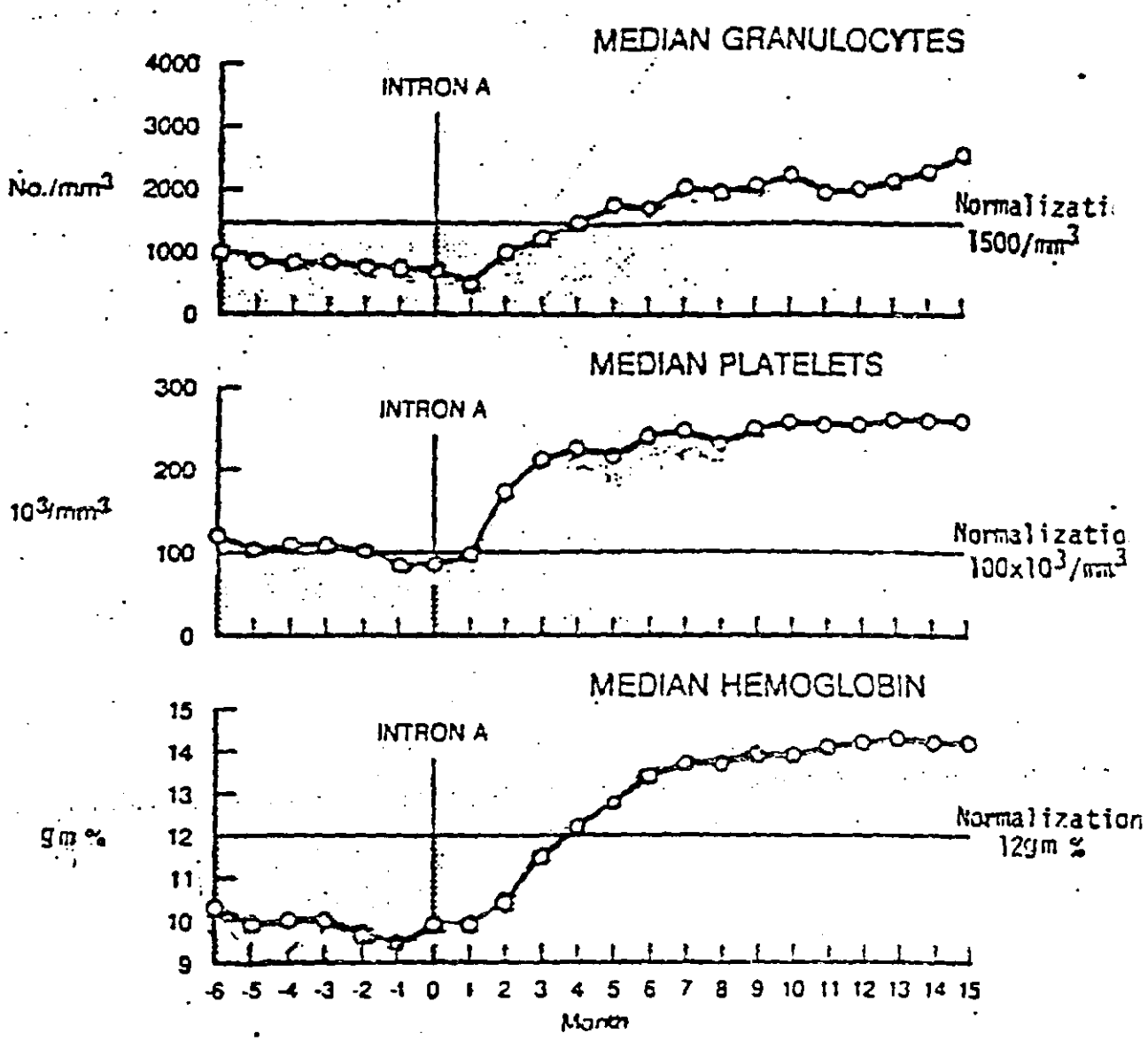

Figure 1. Median values for the three hematologic variables for patients in the INTRON A study.

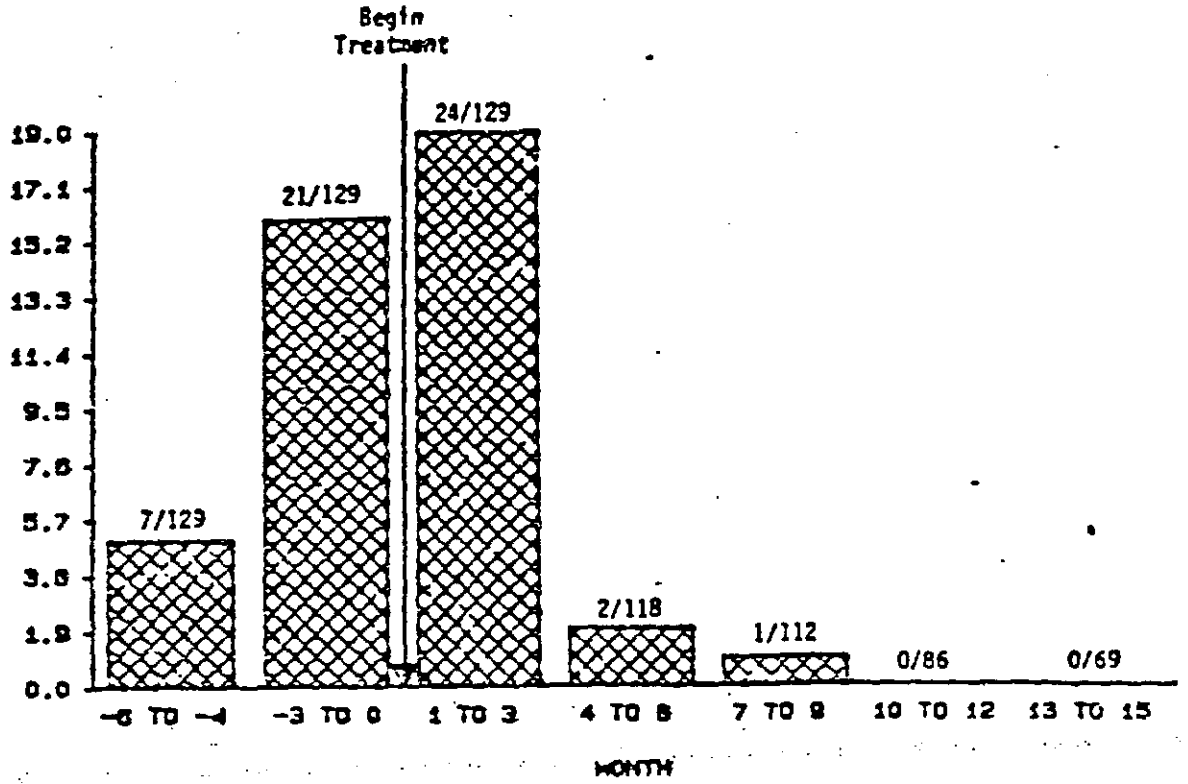

Figure 2. Percent of patients in the INTRON A study requiring platelet transfusions.

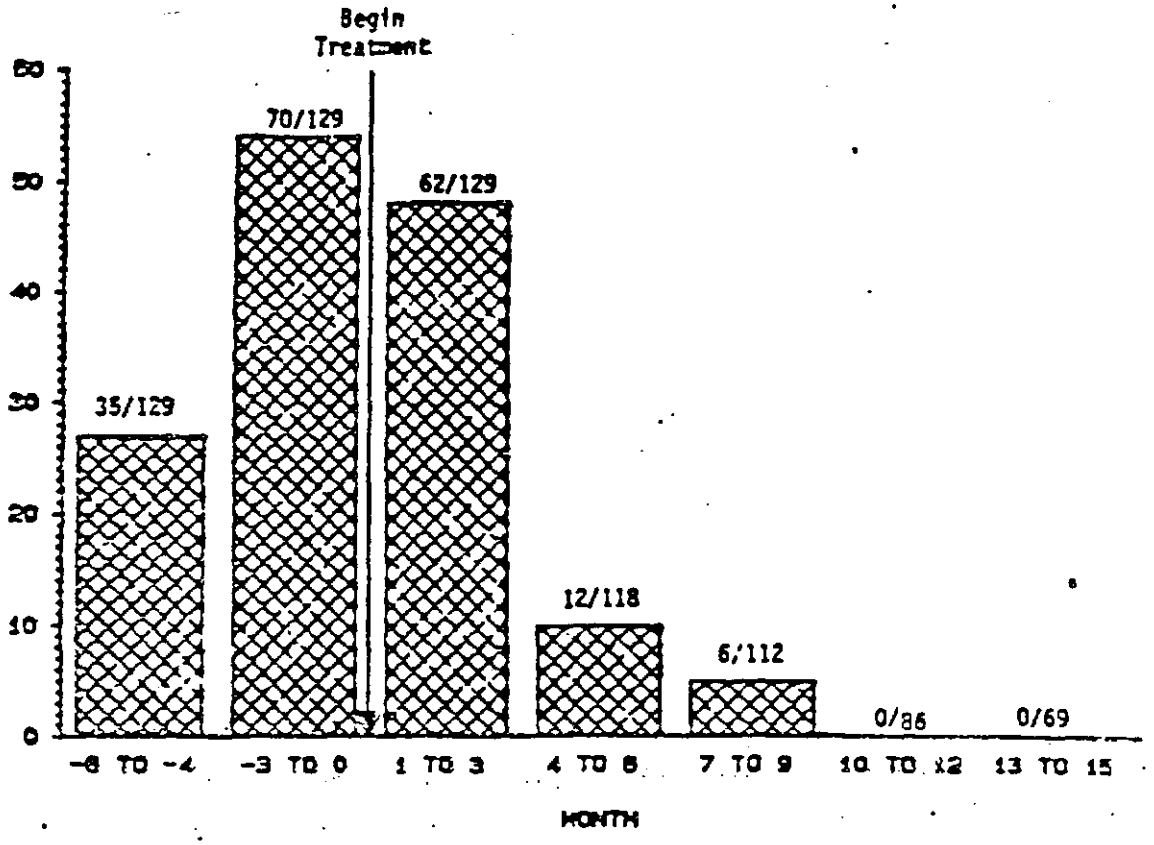

Figure 3. Percent of patients in the INTRON A study requiring red blood cell transfusions.

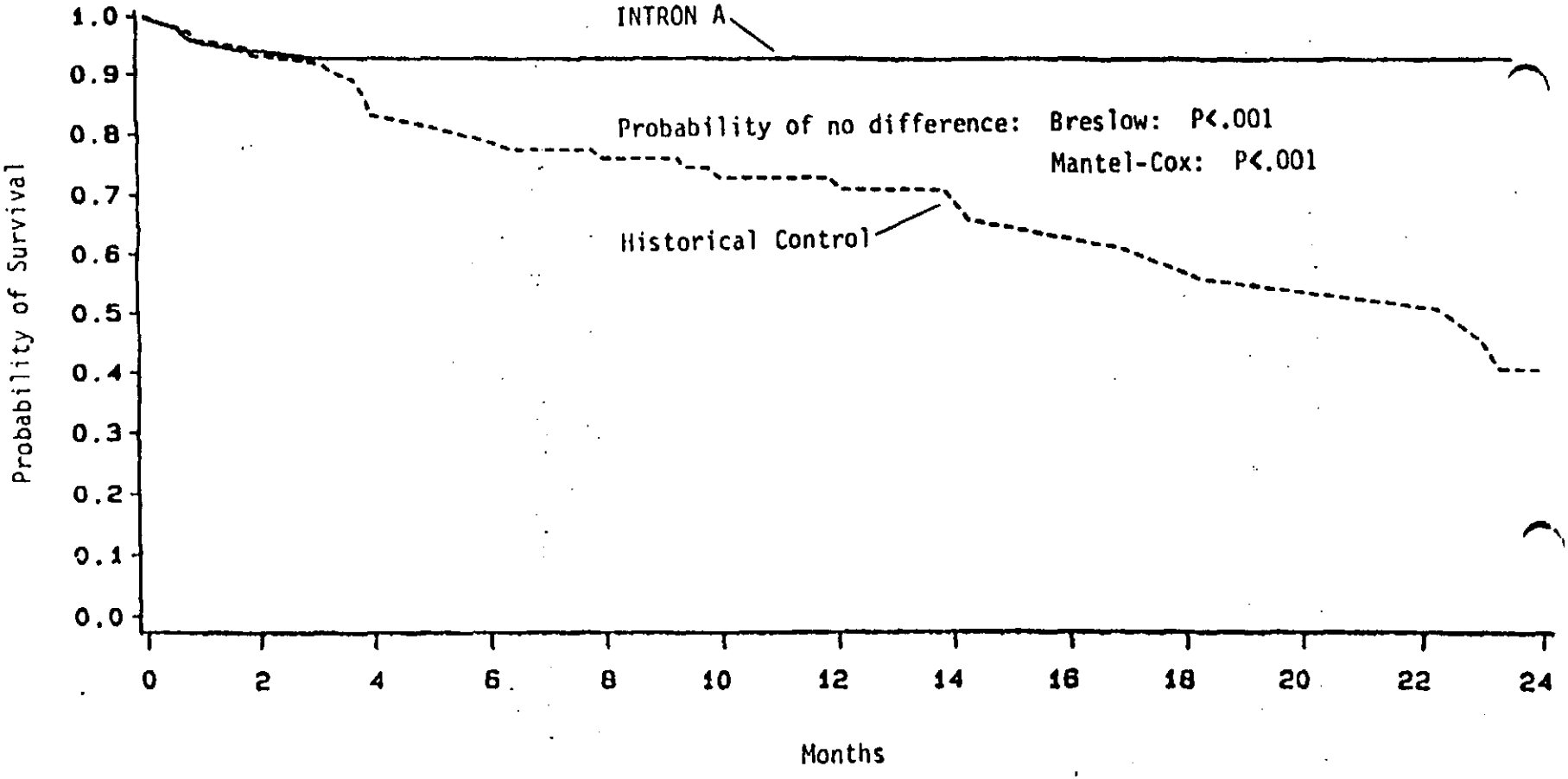

Figure 4. Kaplan-Meier estimated survival curves for the 145 INTRON A-treated patients and 71 patients treate with standard, historical therapies.

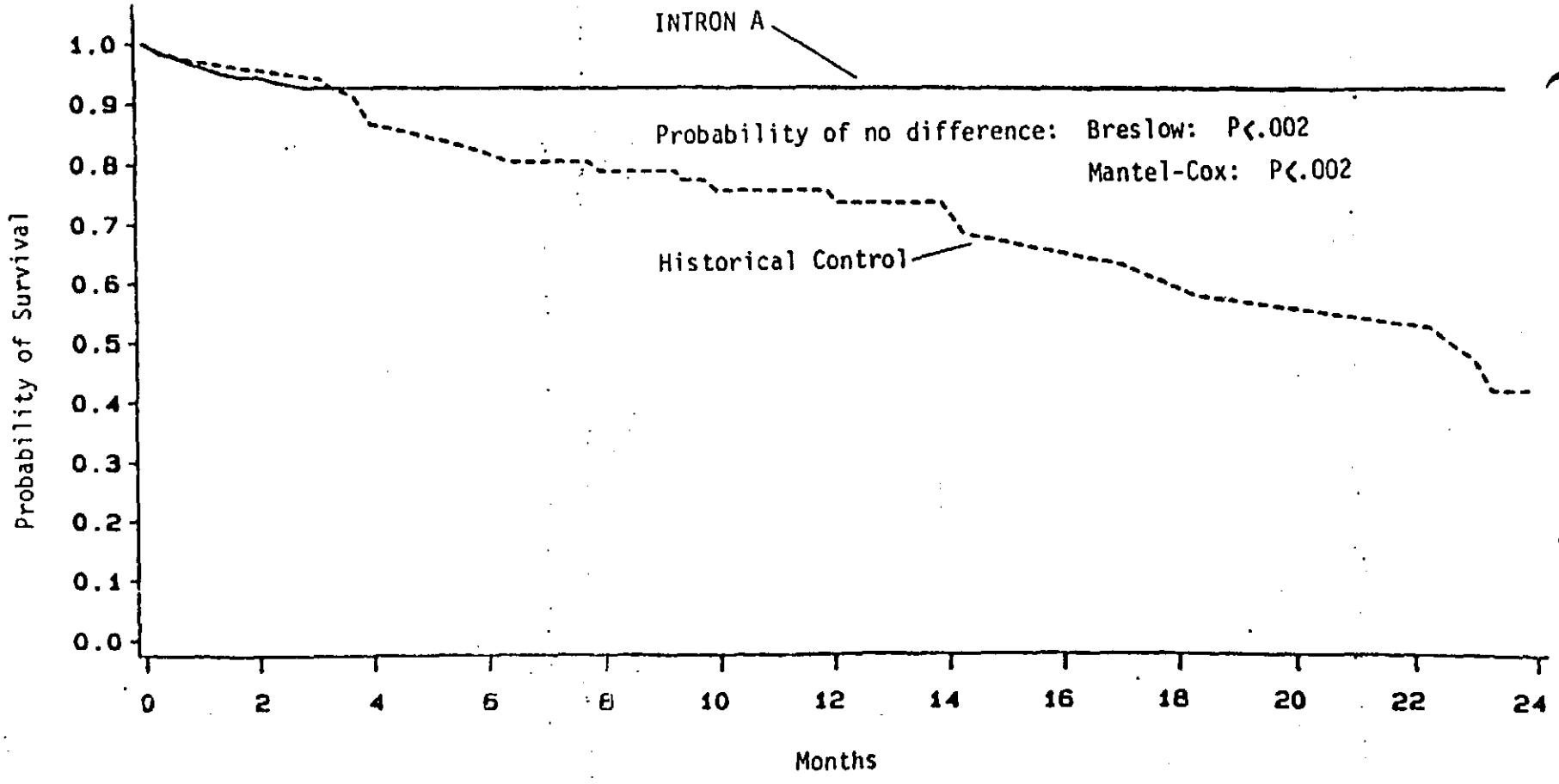

Figure 5. Kaplan-Meier estimated survival curves for the 121 splenectomized INTRON A-treated patients and the 67 splenectomized historical control patients.

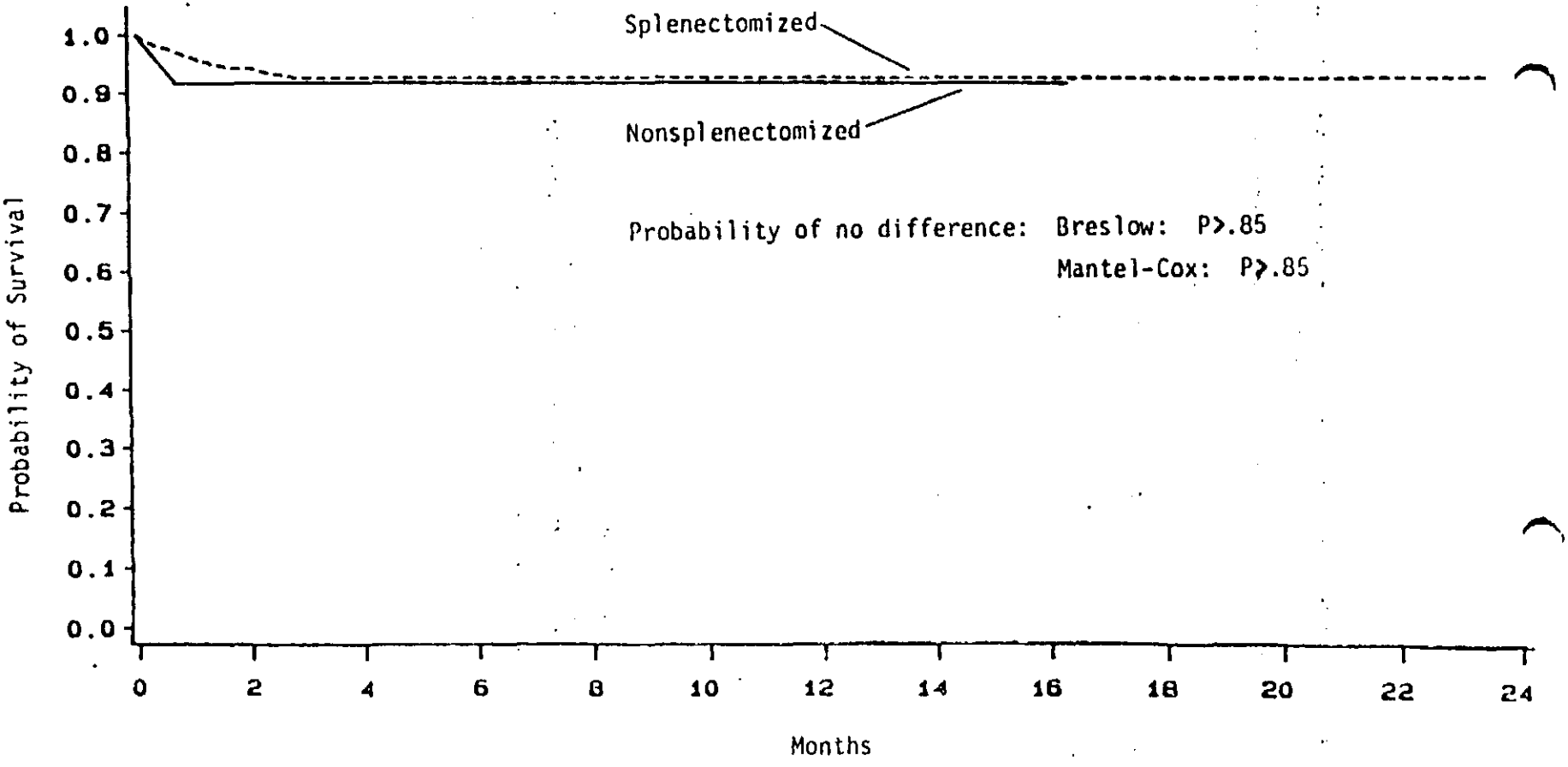

Figure 6. Kaplan-Meier estimated survival curves for the 121 splenectomized and 24 nonsplenectomized patients who received INTRON A.

Exhibit 1

F-13762805 **PRODUCT INFORMATION**

INTRON® A

Interferon alfa-2b recombinant

For Injection

DESCRIPTION INTRON A Interferon alfa-2b, recombinant for injection is a purified sterile, lyophilized recombinant interferon formulated for use by intramuscular or subcutaneous injection (see **PRECAUTIONS**).

INTRON A is a water soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. Interferon alfa-2b is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of INTRON A is approximately 2×10^8 IU/mg protein.

The content of INTRON A is expressed in terms of International Units (IU). International Units are determined by comparison of the antiviral activity of the interferon alfa-2b, recombinant with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organization (WHO).

Each vial of INTRON A contains either 3 million, 5 million, 10 million, or 25 million IU of interferon alfa-2b, recombinant; glycine, sodium phosphate dibasic, sodium phosphate monobasic, and human albumin are also present. Based on the specific activity of INTRON A as approximately 2×10^8 IU/mg protein, the corresponding mg quantities of interferon alfa-2b, recombinant in the vials described above are approximately 0.015 mg, 0.025 mg, 0.05 mg and 0.125 mg/protein, respectively. Prior to administration, the lyophilized powder is to be reconstituted with Diluent for INTRON A Interferon alfa-2b, recombinant (bacteriostatic water for injection) provided (see diluent label for preservative). (See **DOSAGE AND ADMINISTRATION**.)

Lyophilized INTRON A is a white to cream colored powder.

CLINICAL PHARMACOLOGY *General* The interferons are a family of naturally occurring, small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or to various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta and gamma. These three classes are not homogeneous, and each may contain several different molecular species of interferon. As an example, at least 14 genetically distinct human alpha interferons have been identified; thus far, INTRON A has been classified as an alfa interferon.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Preliminary studies to characterize these membrane receptors and to determine the subsequent fate of the human interferon-receptor complex have been carried out using ^{125}I-labeled interferon alfa-2b, recombinant. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric membrane proteins. They exhibit selectivity for human but not murine interferons, suggesting species-specificity. Studies with other interferons have demonstrated varying degrees of species-specificity.

The results of several studies suggest that once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation, and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any of these activities might contribute to interferon's therapeutic effects.

Preclinical Pharmacology INTRON A has exhibited antiproliferative effects in preclinical studies employing both cell culture systems and human tumor xenografts in animals, and has demonstrated significant immunomodulatory activity *in vitro*. The clinical significance of these findings is unknown.

The antiproliferative activity of INTRON A Interferon alfa-2b, recombinant for injection was evaluated *in vitro* using mouse and human leukemia cell lines and human osteosarcoma, melanoma and normal amnion cells. No activity was seen in mouse leukemia cells, which argues against species-specificity.

The immunomodulating activity of INTRON A was demonstrated *in vitro* by its augmentation of the spontaneous ("natural killer") activity of human lymphocytes and its enhancement of the tumoricidal activity of human monocytes against human tumor cells. These effects appear to be dose-dependent.

In vivo studies of INTRON A showed inhibition of tumor growth. INTRON A injected *intralesionally* (0.2 million or 0.8 million IU once daily for 7 days) delayed the development and reduced the volume of human osteosarcoma implants in athymic mice. The effect was dose-related. Additionally, *subcutaneous* administration of INTRON A at a dose of 0.2 million IU/day inhibited the growth of implanted human breast tumor xenografts in athymic mice by about 50% after 23 days. INTRON A has not been shown to be effective in the treatment of osteosarcoma or carcinoma of the breast in humans.

Pharmacokinetics The pharmacokinetics of INTRON A were studied in healthy male volunteers following single 10 million IU doses administered intramuscularly, subcutaneously, and as a 30 minute intravenous infusion. The mean serum level concentrations of interferon following intramuscular and subcutaneous injections were comparable. The maximum serum levels obtained via the intramuscular and subcutaneous routes were approximately 150 to 180 IU/ml 6 to 8 hours after administration. The elimination half-lives of interferon following both intramuscular and subcutaneous injections were approximately 6 to 7 hours. Serum levels were below the detection limit of 25 IU/ml 24 hours after the injections. After intravenous administration, serum levels of interferon peaked (546 IU/ml) by the end of the infusion, then declined rapidly with time, becoming undetectable 4 hours after the infusion.

Following a single dose of 10 million IU of INTRON A, by any of the three routes of administration, interferon could not be detected in urine. Preliminary studies with isolated and perfused rabbit kidneys have shown that the kidney may be the main site of interferon catabolism. In addition, the kidney is important in catabolizing proteins with molecular weights below 50,000 daltons.

Hairy Cell Leukemia In clinical trials in patients with hairy cell leukemia, there was depression of circulating red blood cells, white blood cells and platelets during the first one to two months of treatment with INTRON A. Subsequently, both splenectomized and non-splenectomized patients with hairy cell leukemia, treated with INTRON A achieved substantial and sustained improvements in granulocytes, platelets, and hemoglobin levels in 75% of treated patients and at least some improvement (minor responses) occurred in 90%. For the entire study group, median platelet counts were within the normal range after 2 months, median hemoglobin levels were in the normal range after 4 months and median granulocyte counts were in the normal range after 5 months of treatment. Responses of blood cell elements were similar in splenectomized and non-splenectomized patients except that median platelet counts after maximum response was to a level of 100,000 mm^3 in the latter group.

Treatment with INTRON A resulted in a decrease in bone marrow hypercellularity and hairy cell infiltrates. The hairy cell index (HCI), which represents the percent of bone marrow cellularity times the percent of hairy cell infiltrate, was greater than or equal to 50% at the beginning of the study in 87% of patients. The percentage of patients with such an HCI decreased to 25% after six months and to 14% after one year. These results indicate that even though hematologic improvement had occurred earlier, prolonged treatment with INTRON A may be required to obtain maximal reduction in tumor cell infiltrates in the bone marrow.

The percentage of patients with hairy cell leukemia who required red blood cell or platelet transfusions decreased significantly during treatment with INTRON A. Additionally, the percentage of patients with confirmed and serious infections declined during treatment with INTRON A as granulocyte counts improved.

The responses observed in non-splenectomized patients included reversal of splenomegaly and of abnormalities in blood cell counts attributable to hypersplenism. In some cases there was reversal of clinically significant hypersplenism that may have resulted in need for splenectomy.

Reduced risk of major complications of hairy cell leukemia (serious infections, bleeding diatheses, transfusion requirements) were apparent within 3 months of initiation of treatment in comparisons of INTRON A Interferon alfa-2b, recombinant for injection treated patients to a control group. No deaths occurred in patients treated with INTRON A during the subsequent 9 months of treatment and follow-up, while the mortality rate in the control group was 20% in the same time interval based on projection of survival analysis. During the initial 3 months of treatment, there may be interferon-mediated suppression of hematopoiesis.

In a multicenter controlled clinical trial involving 145 hairy cell leukemia patients, no serum neutralizing activity was detected in the 87 patients evaluated. Serum neutralizing activity was detected in some patients treated with higher doses of INTRON A in malignancies other than hairy cell leukemia. The clinical significance of these findings is unknown.

INDICATIONS AND USAGE INTRON A for Injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia. Studies have shown that INTRON A can produce clinically meaningful regression or stabilization of this disease, both in previously splenectomized and non-splenectomized patients.

Prior to initiation of therapy, tests should be performed to quantitate peripheral blood hemoglobin, platelets, granulocytes and hairy cells and bone marrow hairy cells. These parameters should be monitored periodically during treatment to determine whether response to treatment has occurred. If a patient does not respond within 6 months, treatment should be discontinued. If a response to treatment does occur, treatment usually should be continued until no further improvement is observed and these laboratory parameters have been stable for about 3 months (see **DOSAGE AND ADMINISTRATION**). It is not known whether continued treatment after that time point is beneficial. Studies are in progress to evaluate this question.

CONTRAINDICATIONS INTRON A is contraindicated in patients with a history of hypersensitivity to interferon alfa or any component of the injection.

WARNINGS Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases termination of therapy with INTRON A.

Because of the fever and other "flu-like" symptoms associated with INTRON A administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of cardiovascular disease (e.g., unstable angina, uncontrolled congestive heart failure), pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (e.g., thrombocytopenia, pulmonary embolism) or severe myelosuppression.

Patients with platelet counts of less than 50,000 mm^3 should not be administered INTRON A intramuscularly, but instead by subcutaneous administration.

Cardiovascular adverse experiences which include significant hypotension, arrhythmias, or tachycardia of 150 beats per minute or greater, were observed in approximately 3% of the patients studied who had various malignancies and were treated at doses higher than those for hairy cell leukemia. The incidence of these complications in patients with preexisting heart disease is unknown. Hypotension may occur during administration or up to two days post therapy, and may require supportive therapy, including fluid replacement to maintain intravascular volume. Supraventricular arrhythmias occurred rarely and appeared to be correlated with preexisting conditions, and prior therapy with cardiotoxic agents. These adverse experiences were controlled by modifying the dose or discontinuing treatment, but may require specific additional therapy.

Those patients with a recent history of myocardial infarction and/or previous or current arrhythmic disorder who require INTRON A therapy should be closely monitored (see **Laboratory Tests**).

Central nervous system effects manifested by depression, confusion and other alterations of mental status were observed in about 2% of hairy cell leukemia patients treated with INTRON A. The overall incidence in a larger patient population with other malignancies treated with higher doses of INTRON A was 10%. More significant obtundation and coma have been observed in some patients, usually elderly, treated at higher doses for other malignant diseases. These effects are usually rapidly reversible. In a few severe episodes, full resolution of symptoms has taken up to three weeks. Patients should be closely monitored until resolution of these effects. Discontinuation of INTRON A Interferon alfa-2b, recombinant for injection

PRODUCT INFORMATION

INTRON® A

Interferon alfa-2b recombinant

For Injection

therapy may be required. Narcotics, hypnotics, or sedatives may be used concurrently with caution.

Acute serious hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis, etc.) have not been observed in patients receiving INTRON A; however, if such an acute reaction develops, the drug should be discontinued immediately and appropriate medical therapy instituted. Transient cutaneous rashes have occurred in some patients following injection, but have not necessitated treatment interruption.

Laboratory abnormalities which occurred in hairy cell leukemia patients included elevated SGOT and SGPT, which occurred in 4% and 13% of patients, respectively. The overall incidences of laboratory abnormalities in a larger patient population with other malignancies, and treated at higher doses were somewhat higher. These included elevated liver function tests (SGOT, SGPT in 10% of patients) and reductions in granulocyte (20% of patients) and platelet counts (18% of patients) (see **Laboratory Tests**). These abnormalities are usually mild to moderate and transient. Severe abnormalities of these laboratory parameters are usually rapidly reversible upon cessation or reduction of INTRON A therapy.

PRECAUTIONS Information for Patients Patients being treated with INTRON A should be directed in its appropriate use, informed of benefits and risks associated with treatment and referred to the Patient Information Sheet. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be cautioned not to change brands of interferon without medical consultation as a change in dosage may result.

The most common adverse experiences occurring with INTRON A therapy are "flu-like" symptoms such as fever, headache, fatigue, anorexia, nausea, or vomiting (see **ADVERSE REACTIONS** section) and appear to decrease in severity as treatment continues. Some of these "flu-like" symptoms may be minimized by bedtime administration. Acetaminophen may be used to prevent or partially alleviate the fever and headache.

It is advised that patients be well hydrated especially during the initial stages of treatment.

Laboratory Tests In addition to those tests normally required for monitoring patients with hairy cell leukemia, the following laboratory tests are recommended for all patients on INTRON A therapy, prior to beginning treatment and then periodically thereafter:

- Standard hematologic tests — including complete blood counts and differential as well as platelet counts.
- Blood chemistries — electrolytes and liver function tests.

Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of cancer, should have electrocardiograms taken prior to and during the course of treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility Studies with INTRON A have not been performed to determine carcinogenicity or the effect on fertility. Interferon may impair fertility. Mutagenicity studies with INTRON A revealed no adverse effects.

Studies in mice, rats, and monkeys injected with INTRON A for up to one month have revealed no evidence of toxicity. However, due to the known species-specificity of interferon, the effects in animals are unlikely to be predictive of those in man.

Pregnancy Category C Animal reproduction studies have not been conducted with INTRON A. It is also not known whether INTRON A can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. INTRON A should be given to a pregnant woman only if clearly needed. Another interferon alfa preparation has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) when given at 20 to 500 times the human dose. Therefore, INTRON A should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed.

INTRON A (interferon alfa-2b, recombinant for injection) should be used with caution in fertile men and women.

Nursing Mothers It is not known whether this drug is excreted in human milk. However, studies in mice have shown that mouse interferons are excreted into the milk. Because of the potential for serious adverse reactions from INTRON A in nursing infants, 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.

Pediatric Use Safety and effectiveness have not been established in patients below the age of 18 years.

ADVERSE REACTIONS Adverse reactions to INTRON A are dose-related. In studies of patients with malignancies other than hairy cell leukemia, hematologic and hepatic toxicities were more common in patients receiving individual injections greater than 10 million IU, than in patients receiving less than this amount. Hematologic, hepatic, cardiovascular and neurologic toxicities were more common in patients receiving more than 30 million IU per injection than in patients receiving less than that amount.

The following adverse reactions were reported to be possibly or probably related to INTRON A therapy during clinical trials. The most frequently reported adverse reactions were flu-like symptoms, primarily fever, fatigue, and chills which occurred in almost all patients treated. Other organ systems in which reactions occurred in more than 5% of the patients are:

General — Taste alteration, anorexia and weight decrease occurred uncommonly.

Cardiovascular — Mild hypotension was frequently recorded although it was rarely symptomatic. Hypertension also occurred less commonly. Tachycardias occurred uncommonly usually in association with high fevers.

Gastrointestinal System — Nausea was common, although vomiting occurred rarely. Mild diarrhea was reported less commonly.

Hematologic — Mild thrombocytopenia and transient granulocytopenia occurred commonly.

Musculo-Skeletal System — Myalgia and arthralgia occurred commonly, usually in association with other flu-like symptoms.

Nervous System — Headache, somnolence, confusion, and dizziness occurred uncommonly. Ataxia and paresthesia were rare.

Psychiatric — Anxiety, depression and nervousness occurred uncommonly.

Skin and Appendages — Mild pruritus occurred uncommonly. Mild alopecia was uncommon. Various transient, mild skin rashes were seen frequently in patients with hairy cell leukemia.

Other Adverse Reactions — The following adverse reactions were reported with an incidence of 5% or less: leg cramps, constipation, insomnia, herpetic eruptions, non-herpetic cold sores, urticaria, hot flashes, supraventricular arrhythmias, epistaxis, stomatitis, paralytic ileus, dehydration, coagulation disorder (elevated PT and PTT), abnormal vision, tremor, emotional lability, chest pain, pharyngitis and syncope.

Adverse reactions reported rarely (less than 1%) were dyspnea, purpura, dysphea, sneezing, oculomotor paralysis, nasal congestion, flatulence, increased salivation, hyperglycemia, and ulcerative stomatitis.

Laboratory Value Changes — Those patient laboratory values which were normal to moderately abnormal (WHO grades 0–2) at baseline that worsened to either severe or life-threatening abnormalities (WHO grades 3 or 4) during some phase of treatment included WBC, platelets, granulocytes, SGOT, creatinine, SGPT, LDH, and alkaline phosphatase.

DOSAGE AND ADMINISTRATION The recommended dosage of INTRON A for injection for the treatment of hairy cell leukemia is 2 million IU/m² administered intramuscularly (see **WARNINGS**) or subcutaneously 3 times a week. Higher doses are not recommended. The normalization of one or more hematologic variables usually begins within 2 months of initiation of therapy. Improvement in all three hematologic variables may require 6 months or more of therapy.

This dosage regimen should be maintained unless the disease progresses rapidly or severe intolerance is manifested. If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If persistent or recurrent intolerance develops following adequate dosage adjustment or disease progresses, treatment with INTRON A (interferon alfa-2b, recombinant for injection) should be discontinued. The maximum effective dose of INTRON A has not been established.

At the discretion of the physician, the patient may self-administer the dose. The medication may be administered at bedtime.

Preparation and Administration of INTRON A

Reconstitution of lyophilized INTRON A for Injection Using a sterile syringe and needle, inject the amount of Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) stated in the chart below, into the vial of INTRON A. Agitate gently to hasten complete dissolution of the powder. The appropriate dose of INTRON A should then be withdrawn with a sterile syringe and injected intramuscularly or subcutaneously.

Vial Strength	*ml Diluent*	*Final Concentration*
3 million IU	1	3 million IU/ml
5 million IU	1	5 million IU/ml
10 million IU	2	5 million IU/ml
25 million IU	5	5 million IU/ml

Stability After reconstitution with Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) the solution is stable for one month at 2° to 8°C (36° to 46°F). The reconstituted solution is clear and colorless to light yellow.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

INTRON A may be administered using either sterilized glass or plastic disposable syringes.

HOW SUPPLIED INTRON A (interferon alfa-2b, recombinant for injection) 3 million IU per vial and Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) 1 ml per vial: boxes containing 1 vial of INTRON A for injection and 1 vial of Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) (NDC 0085-0647-03).

INTRON A (interferon alfa-2b, recombinant for injection, 5 million IU per vial and Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) 1 ml per vial; boxes containing 1 vial of INTRON A for injection and 1 vial of Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) (NDC 0085-0120-02).

INTRON A (interferon alfa-2b, recombinant for injection, 10 million IU per vial and Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) 2 ml per vial; boxes containing 1 vial of INTRON A for injection and 1 vial of Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) (NDC 0085-0574-02).

INTRON A (interferon alfa-2b, recombinant for injection, 25 million IU per vial and Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) 5 ml per vial; boxes containing 1 vial of INTRON A for injection and 1 vial of Diluent for INTRON A (interferon alfa-2b, recombinant (bacteriostatic water for injection) (NDC 0085-0285-02).

Store INTRON A for Injection, both before and after reconstitution, between 2° and 8°C (36° and 46°F).

Schering Corporation
Kenilworth, NJ 07033 USA

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PATIENT INFORMATION SHEET

INTRON® A
Interferon alfa-2b, recombinant
For Injection

INFORMATION FOR THE PATIENT
For Subcutaneous Administration

CONSULT YOUR PHYSICIAN REGARDING POTENTIAL ADVERSE EFFECTS OF INTRON A. IF ADVERSE EFFECTS OCCUR, CONSULT YOUR PHYSICIAN REGARDING CONTINUING THERAPY.

DO NOT CHANGE TO ANOTHER BRAND OF INTERFERON WITHOUT CONSULTING YOUR PHYSICIAN AS THIS MAY RESULT IN A CHANGE IN DOSAGE.

DO NOT MIX (RECONSTITUTE) THE DRUG, OR INJECT IT, UNTIL YOUR PHYSICIAN HAS THOROUGHLY TRAINED YOU IN THE PROPER TECHNIQUES.

If you have any questions, contact your physician prior to reconstituting or injecting INTRON A.

Reconstitute the vials of INTRON A for Injection only with the Diluent for INTRON A Interferon alfa-2b, recombinant (bacteriostatic water for injection), which is provided.

Use the sterile technique as instructed by your physician. Destroy disposable syringes and needles after each use and discard appropriately.

RECONSTITUTING INTRON A

Reconstituting means adding a liquid (diluent) to a dry powder. In this case, INTRON A for Injection must be mixed with bacteriostatic water for injection, the sterile diluent provided, before it can be injected.

To prepare the INTRON A solution:

1. With pencil or pen, mark the date you add the diluent in the space provided on the INTRON A vial.

2. Wash your hands thoroughly with soap and water, rinse, and towel dry.

3. Remove the protective plastic cap from the top of both the diluent and INTRON A vial. Clean the rubber stopper on the top of each vial with an alcohol swab.

4. Your physician will tell you what size syringe and needle to use for mixing and how much diluent to add to the INTRON A vial. The amount of diluent will vary depending on which INTRON A concentration is used.

5. Remove cap from syringe needle and fill with air by pulling the plunger to the level indicated by your physician (Figure A).

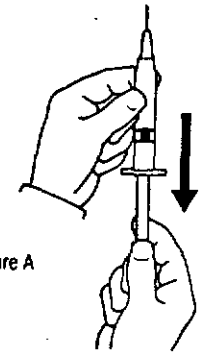


Figure A

Hold the vial upright without touching the top of the cleaned vial with your hands (Figure B).

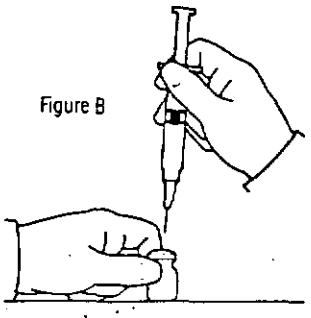


Figure B

Insert the needle into the vial containing the diluent and inject the air into the vial (Figure C).

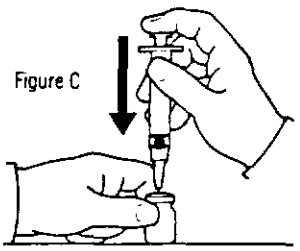


Figure C

Invert the vial, and make sure the tip of the needle is in the liquid. Withdraw the diluent, to be added to the INTRON A vial, by pulling the plunger to the exact amount your physician has told you (Figure D).

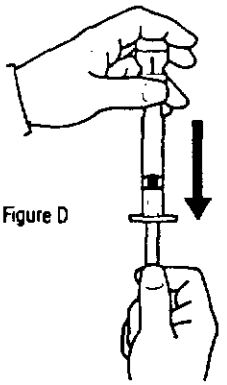


Figure D

The marks on the side of the syringe indicate the amount of diluent withdrawn. Withdraw the needle from the vial (Figure E).

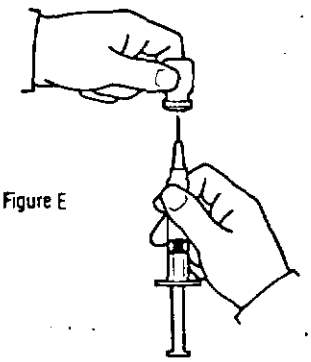


Figure E

6. To prepare INTRON A, insert the needle through the rubber top of the INTRON A vial and gently place the needle tip against the glass wall of the vial (Figure F).

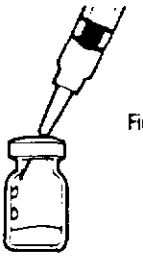


Figure F

continued on back

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. DO NOT AIM THE STREAM AT THE WHITE POWDER at the bottom of the vial.

Remove the needle from the vial and replace the needle cap. To dissolve the white contents, swirl the vial of INTRON A with a gentle rotary motion (Figure G), until the contents are completely dissolved. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before injecting the dose.

Figure G

7. **IMPORTANT:** Before each use, the liquid in the vial should be clear, colorless to light yellow, and without particles. Do not use if you see particles or the color is not correct and call your physician, nurse or pharmacist.

STORAGE OF INTRON A

Before and after reconstitution, INTRON A should be stored in the refrigerator at 2° to 8° C (36° to 46° F), *not* in the freezer. INTRON A should not be used one month after the date you added the bacteriostatic water for injection. Any INTRON A remaining after one month should be discarded.

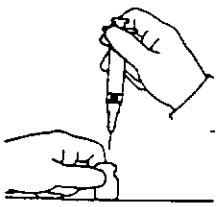
PREPARING THE INTRON A DOSE

— If immediately after reconstituting INTRON A you are removing the first dose from the vial, remove the cap from the needle and put the needle through the rubber top of the INTRON A vial. Proceed to number 4.

— For subsequent doses from the INTRON A vial, start from number 1.

1. Wash your hands thoroughly.

2. Clean the rubber stopper on the top of the INTRON A vial with an alcohol swab.



3. Remove the plastic cap from the needle. Put the needle through the rubber top of the INTRON A vial (Figure H).

Figure H

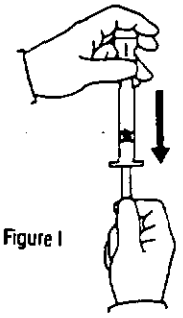


Figure I

4. Turn bottle and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the correct dose as prescribed by your physician, into syringe (Figure I).

5. Check for air bubbles in the syringe. Too large an air bubble will reduce the dose. To remove air bubbles, with the needle still in the vial, slowly push the INTRON A solution back into the bottle above the fluid level and remeasure your correct dose.

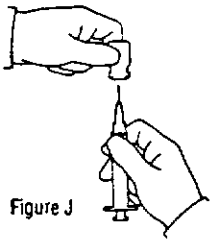


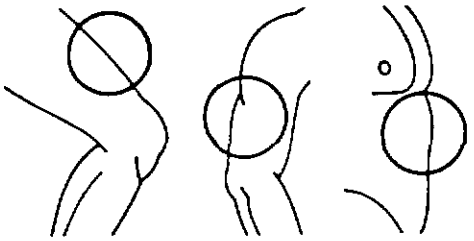
Figure J

6. Double check your dose. Remove needle from bottle (Figure J). Cover needle with cap. If the solution is cold, warm syringe between hands. Lay syringe down on a flat surface so that needle does not touch anything.

INJECTING THE DOSE:

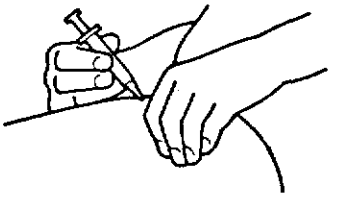
1. Selecting the Site for Injection

- The best site for injection is tissue with a layer of fat between skin and muscle
  - — thigh
  - — outer surface of the upper arm
  - — abdomen, except the navel or waistline.
- If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
- Do not inject INTRON A in the same place repeatedly — rotate your injection sites in a regular pattern.



2. With one hand, pinch a 2 inch fold of skin. Cleanse the skin where the injection is to be made with an alcohol swab. Wait for area to dry. Remove cap from needle.

3. Pick up syringe with other hand, and hold it as you would a pencil. Insert needle straight into the pinched skin (45° to 90° angle).



After the needle is in, remove hand used to pinch skin and use it to hold syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle and insert it in another location. (Follow steps 2 through 3.)

4. If blood does not appear in the syringe, push plunger all the way down gently.

5. Hold alcohol swab near the needle and pull needle straight out of skin. Press alcohol swab over injection site for several seconds. Do not massage injection site. If there is bleeding, cover with an adhesive bandage.

6. Use disposable syringe only once to insure sterility of syringe and needle. Destroy syringe and needle as directed.

7. After two hours, check injection site for signs of inflammation, such as redness, swelling, or tenderness; if there are any, contact your physician or nurse.

Schering

Schering Corporation
Kenilworth, NJ 07033 USA

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