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.

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^{o}-8^{o}C for the lyophilized product and one month at 2^{o}-8^{o}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.

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).

[illegible] of 2.6x10 [illegible] (SC) and [illegible] 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.