A MULTI-CENTER RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFECT OF ISOPRINOSINE® IN IMMUNODEPRESSED PATIENTS WITH UNCOMPLICATED GENERALIZED LYMPHADENOPATHY

PROTOCOL

NPII 006.3*

NEWPORT PHARMACEUTICALS INTERNATIONAL, INC.
897 West Sixteenth Street
P.O. Box 1990
Newport Beach, California 92658-8935

November, 1984

I have read and agree to follow the procedures as outlined in this protocol.

_____ _____

Investigator Date

* Amendment to NPII 006.2

A MULTI-CENTER RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFECT OF ISOPRINOSINE® IN IMMUNODEPRESSED PATIENTS WITH UNCOMPLICATED GENERALIZED LYMPHADENOPATHY

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ABSTRACT

I. A multI-center, randomized, double-blind, placebo-controlled study to investigate the effect of isoprinosine (inosine pranobex) in immunodepressed patients with uncomplicated generalized lymphadenopathy.

II. Objective: To determine if isoprinosine produces a significant immunorestorative effect within the study observation period (90 days) as measured by an increase in one or more of the following: NK cell activity, total T-cells and T-helper cells.

III. Patient Eligibility:
   a. Patients who are at high risk for developing AIDS.
   b. Patients 18 to 50 years of age with prolonged generalized lymphadenopathy for more than 3 months.
   c. Patients who have a T-cell helper/suppressor ratio between 0.4 and 0.9 $\pm$ 0.1 and/or an absolute T-cell helper number of 700/mm3 or below.
   d. NK cell function below 18 or a value that is less than a value 1 standard deviation lower than the mean value for normal subjects as determined by the particular laboratory.

IV. Study Design: Patients will have a complete immune evaluation to establish a baseline prior to the start of treatment. Patients will be randomly assigned to one of two treatment groups: Isoprinosine or placebo. Patients on Isoprinosine will receive 3 grams daily. The treatment period will be 28 days.

V. Study Evaluations: Patients will receive a complete physical examination at screen and on Day 28. Signs and symptoms relative to uncomplicated generalized lymphadenopathy will be obtained at screen, Day 0, 14, 28 and 90, and also the following laboratory evaluations: T-helper cells, T-suppressor cells, total T cells, NK cell activity, CBC, differential, and SMA 12 (including uric acid). Patients platelet count will be evaluated at screen, Day 0 and 90. P.P.D. skin test will also be carried out at Day 0 and Day 28.

VI. Criteria for Response: Patients must show a significant increase in either NK cell activity, total T cells or T-helper cells within the study observation period.

1.0 Background

Acquired Immunodeficiency Syndrome (AIDS)

AIDS was first observed in the form of an unusually high incidence of Kaposi's sarcoma (KS) and pneumocystis carinii pneumonia (PCP) among homosexual men in New York and California [8]. The first reports in the medical literature described a syndrome characterized by an acquired dysfunction of cellular immunity leading to severe opportunistic infections [21, 31, 42]. As of January 1984, 3,000 cases had been reported to the Center for Disease Control [10]. Forty-three percent of these patients were known to have died. PCP was diagnosed in 51% of the patients while KS was diagnosed in 26%; 7% of the patients had both PCP and KS and 16% had other opportunistic infections without PCP or KS. The great majority of AIDS patients (71%) were male homosexuals while most of the remaining patients could be classified as intravenous drug users (17%), Haitian immigrants (5%) or hemophiliacs (1%).

Patients with AIDS are typically anergic and lymphogenic. Natural killer (NK) cell activity and lymphocyte proliferative responses to mitogens and antigens were also reported to be depressed [21, 31, 40].

Monoclonal antibody analyses of T-cell subpopulations showed a reduced percentage of T-helper cells and sometimes an increased percentage of T-suppressor cells [21]. Reduction of the helper/ suppressor ratio was later reported in asymptomatic homosexuals

and was shown to be related to sexual promiscuity [27] and the practice of passive anal intercourse [14].

Further examination of the male homosexual population revealed a syndrome of chronic unexplained lymphadenopathy and various constitutional symptoms such as fatigue, weight loss, fever and diarrhea [7, 9, 32]. This syndrome, may represent a prodromal stage or a less severe form of AIDS [32]. In general, the immunologic abnormalities seen in AIDS patients are also observed, in a less severe form, among patients with lymphadenopathy [1, 32, 37, 42].

Although AIDS is believed to result, in part, from a transmissible agent (such as: cytomegalovirus, Epstein-Barr virus, hepatitis virus, adenovirus type 35 or human lymphotropic retro viruses [37]). There is some support for the hypothesis of a multi-factorial etiology based on repeated infections and other immunosuppressive factors associated with the sexual practices of the groups at risk [41]. Thus, immunotherapy directed at the cellular immune defect is indicated. Interferon has been used, with mixed results, as a treatment for KS in homosexual males [17, 29]. Treatment with interleukin-2 (IL-2) has been suggested based on its <u>in vitro</u> enhancement of NK cell function, cytomegalovirus specific cytotoxicity, immune interferon release and lymphocyte proliferative responses in AIDS patients [35, 36]. However, presently, these substances have not been established as a safe and effective

agent for the treatment of patients with AIDS or generalized lymphadenopathy.

2.0 Drug Information

ISOPRINOSINE® (inosine pranobex) is a synthetic immunopotentiating agent which has long been known to be capable of *in vitro* enhancement of mitogen-induced lymphocyte proliferation, macrophage activation and T-rosette formation [23, 24, 51]. Recent *in vitro* studies have shown that ISOPRINOSINE induces significant enhancement of NK cell activity [2, 47, 50] and production of interferon [43] and IL-2 [33, 48]. In animal models, ISOPRINOSINE has been shown to produce increased NK cell cytotoxicity [43, 45], restoration of IL-2 production [16] and augmentation of the antitumor effect of interferon [11] as well as increases in survival of animals administered Ehrlich Ascites tumor cells [15], and influenza or herpes virus [20, 34].

In humans, ISOPRINOSINE produces enhanced lymphocyte proliferative responses to mitogens [6, 18] and antigens [13] and increased production of lymphotoxin [6] and interferon [28]. Clinical trials have demonstrated significant activity against infections caused by a number of viruses including influenza [26] herpes simplex [5, 19] and subacute sclerosing panencephalitis [25].

Preliminary studies suggests that ISOPRINOSINE may be useful in the treatment of AIDS. *In vitro* experiments have shown an enhancement of mitogen-induced lymphoproliferative responses in peripheral blood lymphocytes (PBL) from patients with AIDS [30] or lymphadenopathy [49]. IL-2 activity in PBL from AIDS

patients is also increased by *in vitro* addition of ISOPRINOSINE [46]. *In vivo*, ISOPRINOSINE has been shown to be associated with increased NK cell activity in mildly immunosuppressed volunteer subjects [3,4]. In this double-blind placebo-controlled study, immunosuppressed male homosexuals with mild clinical signs and symptoms of prodromal acquired immunodeficiency syndrome (AIDS), received placebo or ISOPRINOSINE at either 1 or 3 grams per day. The study showed ISOPRINOSINE to have immunorestorative properties. Improvement was seen in NK cell activity as well as total T-cell (T-11) and helper cell (T-4) counts. These effects were more marked in patients treated with 3 grams per day for 28 days. The effects lasted lasted for a period of up to 6 months. Normalization of these cellular immune functions may explain the beneficial effects of ISOPRINOSINE in an open label clinical study of patients with pre-AIDS [22]. In that study, symptomatic improvement was observed in patients with pre-AIDS but not in patients with severe AIDS.

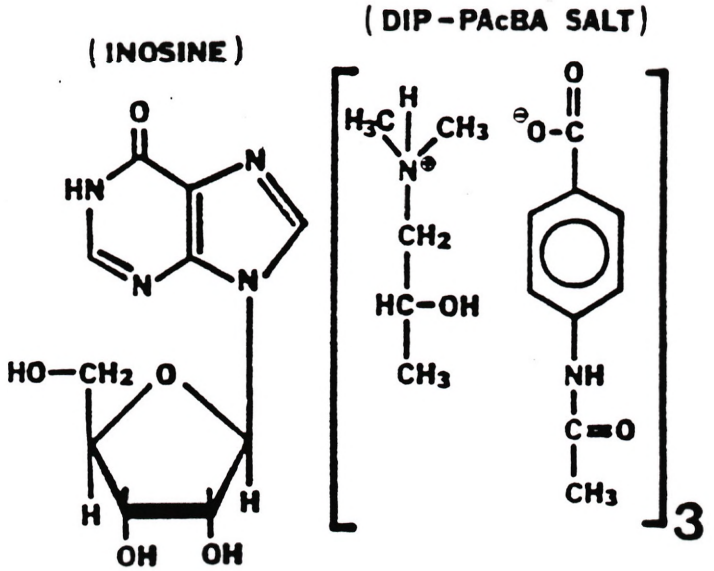
The present double-blind, placebo-controlled clinical trial is designed to verify the efficacy of ISOPRINOSINE in the treatment of uncomplicated generalized lymphadenopathy syndrome in at risk patients.

2.1 Drug Substance

Isoprinosine, the p-acetamidobenzoic acid salt of N,N-dimethylamino-2-propanol:inosine in a 3:1 molar ratio, is a synthetic drug authorized for clinical studies in the United States by the FDA under IND #8980.

The inosine moiety, a naturally occurring purine, is metabolized via normal biochemical pathways to uric acid. This metabolism may cause a slight transitory rise in serum and urine uric acid. The p-acetamidobenzoate moiety is largely metabolized to the glucuronide derivative. N,N-dimethylamino-2-propanol (DIP) is excreted unmetabolized and as the N-oxide.

Structure



ISOPRINOSINE
(Inosine pranobex)

3.0 Objective of Study

The objective of this Phase III, randomized, double-blind, placebo-controlled study in volunteers with immunological deficiency is to determine the effect of isoprinosine in producing an immuno-restorative response within the study observation period (including the two-month period following cessation of the 28 days of treatment), measured by one or more of the following immunological parameters:

3.0.a Increase in NK cell activity

3.0.b Increase in total T-cells (OKT-11)

3.0.c Increases in absolute number and percentages of T-helper cells (OKT-4)

4.0 Study Design

This will be a multi-center, 90-day, single-dose level, double-blind, placebo-controlled study in up to 120 patients (24 per center). The patients will be randomly assigned to one of two treatment groups (Isoprinosine or placebo). The sponsor will provide a computer-generated, randomization code of patient numbers for each center. Patients on drug will receive 3 grams of Isoprinosine daily (two 500 mg tablets t.i.d.) for 28 days. Patients will be evaluated on Days 0 (baseline), 14 and 28 during treatment and again at Day 90, two months after cessation of treatment.

5.0 Patient Population

Up to 120 patients who are capable of comprehending the nature of the study and who will be available for its duration are to be entered into the study provided they conform to the following criteria:

5.1 Inclusion Criteria

5.1.a Patients who have unexplained immunodepression and are at risk of developing AIDS [39]; i.e., homosexual or biosexual men.

5.1.b Patients who are asymptomatic or presenting with one or more of the following prodromal symptoms of AIDS.

1. Fever > 38.5 C(intermittent or continuous) for 3 or more months.
2. Unexplained weight loss (10% body weight or greater than 10 pounds) in the past 3 months.
3. Unexplained recurrent diarrhea over a 3-month period.
4. Unexplained fatigue and diminished mental and/or physical activity.
5. Night sweats for 3 or more months.

5.1.c Patients 18 to 50 years of age with prolonged generalized lymphadenopathy for 3 or more months (greater than 1 cm at two or more noncontiguous sites).

5.1.d Patients are to have a T-cell helper/suppressor ratio of between 0.4 to 0.9 $\pm$ 0.1 and/or an absolute T-cell helper number of 700/mm3 or below.

5.1.e NK cell function below 18 or a value that is les than a value 1 standard deviation less than the mean value for the particular laboratory.

5.2 Exclusion Criteria

5.2.a Patients with Kaposi's sarcoma or overt opportunistic infections as follows:
Candida albicans, Pneumocystis carinii, Herpes simplex, Cryptococcus neoformas, Histo plasma capsulatum, Mycobacterium avium-intracellulare, Toxoplasma gondii, legionela, cryptosporidium, isospora, and papovavirus.

5.2.b Patients with active evidence of infectious mononucleosis caused by Epstein-Barr virus or Cyomegalovirus (CMV) as determined by heterophile test (EBV) or cell culture (CMV).

5.2.c Critically ill patients.

5.2.d Patients receiving steroids, cytotoxic immuno suppressive agents, radiotherapy and/or antiviral medicine prior to the study.

5.2.e Patients who have received any immunomodulators (including Isoprinosine) within one month prior to the start of this study.

5.2.f Patients with a history of gout, uric acid urolithiasis, uric acid nephrolithiasis, renal dysfunction and severe gastric ulcer.

5.2.g Hospitalized patients.

5.2.h Patients who are I.V. drug abusers or hemophiliacs.

5.2.i Women of childbearing age.

5.2.j Patients with lymphoid malignancy.

5.2.k Patients with infectious mononucleosis caused by CMV or EBV.

5.2.l Patients with known heart disease (especially those receiving cardiac glycosides).

5.3 Discontinuation Criteria

5.3.a Development of overt AIDS, Kaposi's sarcoma, and/or opportunistic infections.

5.3.b Administration of systemic antiviral agents or immunomodulating agents.

5.3.c A serum uric acid level of > 9 mg %.

5.3.d Any medical deterioration that the physician considers dangerous to the patient.

6.0 Study Entrance Criteria (Prescreen) (See Study Flow Chart Appendix A)

After completion of a comprehensive history and eligibility form and following an explanation by the investigator about the trial, possible consequences and side effects of the investigational drug, all candidates must read, understand and sign, in the presence of the investigator, the Patient Consent Form (see Appendix C) prior to participation in the clinical trial. A complete physical examination will then be carried out. A biopsy of an enlarged lymph node will be obtained if lymph node malignancy is suspected. Patients with lymphoid malignency are excluded from this study. A blood sample will be obtained for CBC, blood smears, heterophile and/or serology on patients suspected of having active EBV or CMV mononucleosis. Where necessary a culture for CMV or EBV may be required to exclude patient's with CMV or EBV mononucleosis. Patients will also be screened for sexually transmitted diseases on Day 0. Blood samples will be obtained from all patients to satisfy the following:

1.a Patients who have unexplained immunodepression and are at risk of developing AIDS [39]; i.e., homosexual or bisexual men.

1.b Patients who present with one or more mild prodromal symptoms of AIDS, as described in 5.1.b.

1.c Patients 18 to 50 years of age with prolonged generalized lymphadenopathy (greater than one cm at two or more noncontiguous sites).

1.d Patients are to have a T-cell helper/suppressor ratio of between 0.4 and 0.9 $\pm$ 0.1 and/or an absolute T-cell helper number of 700/mm3 or below.

1.e NK cell function below 18 or a value that is less than a

value 1 standard deviation less than the mean value for one particular laboratory.

1.f HTLV III or LAV antibody titer.

6.1 Medical and Laboratory Evaluation

The following medical and laboratory evaluation will be performed on prospective study patients prior to and at appropriate intervals during the study period. (See Appendix)

1.a Hematologic and blood chemistry:

i) CBC and differential

ii) Platelet count

iii) *SMA 12 (includes: total protein, albumin, uric acid creatinine, calcium, inorganic phosphorus, alkaline phosphatase, LDH, SGOT, SGPT, total bilirubin, direct bilirubin. Results of the SMA 12 determinations will be maintained separately from the case report forms until the completion of the study. An independent observer not involved in direct conduct of the study will evaluate this data (SMA-12's) at timely intervals in order to preserve the integrity of the blinded study code and to advise the principal investigator if aberrant values are noted.

1.b Cellular immunity:

i) T-helper cell count (T-4)

ii) T-suppressor cell count (T-8)

iii) Total T-lymphocyte count (T-11)

iv) NK-cell activity

v) PPD skin test

1.c Signs and Symptoms: (Refer to screening form)

i) Vital signs (body wt., temperature, blood pressure, pulse)

ii) Fever

iii) Night sweats

iv) Malaise/fatigue

v) Lymphadenopathy

vi) Arthralgias/myalgias

vii) Weight loss

viii) Other infections

1.d Swollen lymph node locations and measurements.

1.e Complete physical examination.

1.f Any significant adverse reactions.

1.g Serum HTLV III or LAV antibody titers.

*SMA 12 including uric acid will be performed at each visit.

7.0 Study Methods (See Flow Chart, Appendix A)

After prescreening procedures, a patient eligibility form will be completed and all eligible patients will be assigned a number from a randomized list (drug or placebo). This number will coincide with a number on a bottle of tablets to be dispensed to that patient. Codes will be established in multiples of 8 so that there is an equal number in each group treated with Isoprinosine and placebo. Patients are to be placed in the study in numerical order according to the bottle label. Medication will be dispensed with instructions.

7.1 Dosage of Isoprinosine and Placebo

The dosage of Isoprinosine will be 3 grams per day (6 tablets) divided into three doses (morning, afternoon, and evening). The placebo-treated patients will take 6 tablets per day, following the same dosage regimen. This daily regimen will continue for 28 days.

7.2 Concomitant Medications

Other medications that, are considered necessary for the patients' welfare and that will not interfere with the study may be used. Administration of all such drugs must be reported in the appropriate section of the Patient Case Report forms. Uricosuric agents may be administered to

patients with elevated serum uric acid levels at the discretion of the investigator.

7.3 Patient Visits

At the time of patient enrollment (Baseline, Day 0), an appointment schedule will be set. Each patient will receive a reminder of their next scheduled appointments. Patient visits and evaluations will be at screen on and Days 0, 14, 28 and 90.

On the screening and Day 28, each patient will have a complete physical examination. If any clinical observations are abnormal at Day 28, then a complete physical examination will be performed again at Day 90. On Days 0, 14, 28 and 90, patients will be evaluated for the following signs and symptoms relative to uncomplicated generalized lymphadenopathy. Fever, night sweats, malaise or fatigue, chronic lymphadenopathy at 2 or more noncontiguous sites, arthralgias or myalgias, and weight loss of 10 lbs. or 10% of normal body weight. On Day 0 and Day 28, a PPD skin test will be carried out. At each visit, blood will be obtained for appropriate assay procedures (Section 7.4). Any side effects or adverse reactions will be noted at each visit (Section 11.0) and any concomitant medication recorded.

7.4 Assay Procedures

7.4.a - Hematologic and blood chemistry

i) CBC, and differential (each visit)

ii) Platelet Count (Day 0 and 90)

iii) SMA 12 including uric acid (each visit)

7.4.b Cellular Immunity

i) T-helper cell count (T-4) (each visit)

ii) T-suppressor cell count (T-8) (each visit

iii) Total T-lymphocyte count (T-11) (each visit)

iv) NK-cell activity (each visit)

v) PPD skin test (Day 0 and 28)

7.5 Follow-up Examination

The investigator agrees to follow-up examination of the patients at least semi-annually for three years where possible.

8.0 Statistical Approach

In a previous study on immunodepressed volunteers, Isoprinosine was found to potentiate three immune parameters: NK cell activity, number of T-Lymphocytes (T11), and number of T-helper cells (T4). The statistical methodology for estimating patient sample size was designed to accomidate that factor which showed the lowest degree of difference from control; namely, the potentiation of T-helper cells in which the mean difference scores indicating increases from Day 0 were -5 ($\pm$ 207 S.D.) in the placebo group and 141 ($\pm$ 226 S.D.) in the group that received 3 gm/day of Isoprinosine. Also in that clinical trial, 63 of the 74 patients completed the study. Based on this dropout rate, we can predict a final sample size of approximately 102 of the 120 patients admitted to the study. With an expected degree of difference the same as that observed in the previous study and a 2-sided alpha level of 0.05, the beta value (Type II error) is calculated to the approximately 0.07. Therefore, the power of study to reject the null hypothesis is 0.93.

Statistical comparisons on immune parameters will use Student's t test with a two-sided alpha level of 0.05. If there are no significant pre-treatment differences between groups, drug and placebo treated patients will be compared on an increase score obtained by subtracting the value on Day 0 from the value obtained on any given patient examination. Several clinical parameters which yield continuous variables (body weight, temperature, size of enlarged lymph nodes) will be analyzed in a similar fashion.

Signs and Symptoms which are characterized as "severe", "moderate", "mild", or "absent", and the overall clinical evaluation which is characterized as "improved", "same", or "worse" will be scored as ordinal scales and analyzed using the nonparametric Mann-Whitney U test.

9.0 Clinical Material Information

9.1 Study Drugs

Isoprinosine is supplied in 500 mg scored white tablets. A placebo consisting of a tablet without active drug similar in size, shape, and color to the Isoprinosine tablets will be used. The identity of the medication will be blinded to investigator and patient. Coded bottles of medication are supplied to the investigator. Each bottle has a detachable label (flag label) which must be attached to the Patient's Case Report Form and the date the drug was dispensed indicated on the label. The investigator will be provided with sufficient bottles for each patient to complete the entire trial. Patients will be given enough tablets to complete the entire dosage period (i.e., 28 days from admission).

9.2 Code Envelopes and Study Medications

A set of individually sealed envelopes will be provided to the investigator along with the bottles of medication. The envelopes carry the patient number on the outside and the medication code inside, and may be referred to by the investigator only in case of an emergency necessitating identification of the drug.

Opening any envelopes will destroy the blind code for that patient only. At that time, the patient will be dropped from the study. However, appropriate follow-ups of the patients should be done if possible. The investigator will

return all sealed envelopes at the conclusion of the study. The double-blind code will be provided to the investigator only after all analyses have been completed.

The investigator will promptly notify the sponsor by telephone if the code for any patient is broken. In addition, a Medication Code Sheet will be kept on file at the Clinical Research Department, Newport Pharmaceuticals International, Inc.

9.3 Assignment of Study Medications

Patients who meet the criteria and conditions for entry will be placed in the study in numerical order according to the bottle label.

9.4 Drug Accountability

The investigator must maintain accurate records of the receipt of all study medication shipped by the sponsor including date and code numbers received. In addition, accurate records must be kept on the amount and date that medication, by code number, was dispensed or returned for each patient in the trial. The drug accountability records completed by the investigator are to be obtained at the end of therapy (Day 28). A separate page of the Case Report Form for each patient will be provided for the purpose of maintaining this record. Records of all drug supplies received, used and returned must be kept by the principal investigator. All unused drug supplies as

well as all labeled drug containers, where appropriate, will be returned to the sponsor as soon as practical upon completion of the regimen for each patient. Drug accounting procedures must be completed before the study is considered terminated.

10.0 Informed Consent (See Appendix C)

A properly executed, written informed consent in compliance with 21 CFR 50 shall be obtained from each patient prior to entering the trial. A copy will be provided to the patient and a copy shall be maintained in the patient's medical record. In addition, a copy of the signed Informed Consent Form will become an integral part of each Case Report Form provided to the sponsor. The Informed Consent document to be used will be submitted by the investigator to the Institutional Review Board for approval prior to the start of the study.

11.0 Adverse Experiences

11.1 Serious Adverse Experience

11.1.a Any serious adverse experience, whether ascribed to the drug or not, will be communicated promptly, by telephone, to the IRB and sponsor (Clinical Monitor). The investigator should make a detailed written report (1639 FDA form) of any serious adverse experience to the Institutional Review Board and sponsor no later than ten working days after the investigator discovers the adverse effect. Any patients who are withdrawn from the study due to adverse experiences will be followed until their medical outcome is determined and written reports will be provided by the investigator to the sponsor.

11.1.b All adverse experiences regardless of severity and whether or not ascribed to the drug, are to be recorded in the appropriate section of the Case Report Form.

11.2 Adverse Experience Considerations

Since the inosine moiety of Isoprinosine is converted to uric acid in human metabolism, one would expect there may be some degree of increase in uric acid levels of patients treated with the drug. This has, in fact, been found to be true in most cases, and predictably, the amount of increase appears

to be dose-related. It should be pointed out that there have not been any clinical indications of adverse reactions as a result of elevations in serum uric acid. In addition, the length of treatment with Isoprinosine has not been associated with adverse clinical effects as a result of the slightly elevated uric acid levels.

11.2.a Contraindications

i) None known

11.2.b Warnings

i) Because the purine (inosine) moiety of Isoprinosine is rapidly catabolized to uric acid, resulting in elevations of serum and urinary uric acid, Isoprinosine should be used with caution in patients with a history of gout, uric acid urolithiasis, uric acid nephrolithiasis, or renal dysfunction.

11.3 Overdosage

There are no reported cases of overdose of Isoprinosine and therefore signs and symptoms associated with overdose of the drug are not known. Overdosage is unlikely to occur due to the high oral LD_{50} (greater than 5000 mg/kg) reported in the mouse, rat, guinea pig, and cat. However, in the event of overdose, monitoring of potentially elevated urine and serum uric acid levels and administration of uricosuric agents, if necessary, would be recommended.

12.0 Disposition of Data

12.1 Patient Case Report Forms

Immediately on completion of the study, the completed signed and dated Patient Case Report forms shall be submitted to the sponsor for review and statistical analysis. The sponsor may periodically collect data for evaluation during the study.

12.2 Record Retention

The investigator shall maintain all patient records for whichever of the following periods is shortest:

12.2.a A period of two years after the date on which the FDA approves the marketing of the drug for the purposes that were the subject of the study.

12.2.b A period of five years after the date on which the results of the study are submitted to the FDA in support of the marketing of the drug for the purpose that was the subject of the study.

12.3 Investigator Analysis Not Required in Protocol

Additional observations which are of interest to the investigator, but not pertinent to the objectives and analysis of the present study, will be included in the sponsor's case report forms.

12.4 Study Monitoring

The investigator will allow a representative of the sponsor's monitoring team to inspect all Patient Case Report forms and corresponding portions of a patient's original hospital medical records to verify the accuracy and completeness of the study at regular intervals throughout the study.

12.4.a Compliance

i) The monitor will assess patient compliance with regard to taking investigational drug. For example, tablet count will be recorded on each patient's drug accountability form. Patient and investigator compliance will be considered in the evaluation of results.

13.0 Study Protocol Review

Investigator

The acceptance of the protocol and initiation of the study by an institution requires the approval by the governing Institutional Review Board (IRB). Assurance that the IRB approval has been received will be provided to the study sponsor prior to initiation of the study.

Sponsor

The Therapeutic Review Committee at Newport Pharmaceuticals reviews and approves all protocols. Among other things, the Committee reviews the protocols for study design, appropriateness of patient admission and exclusion, adequacy of the Patient Consent Form, compliance status of preclinical studies, and the compliance status of laboratories and facilities which may be used for certain aspects of the clinical study.

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APPENDICES

APPENDIX A

PROTOCOL SUMMARY

	Pre-Treatment Period	Treatment Period			Post-Treatment Period
	Screen	Baseline			
DAY	-14 or less	0	14	28	90
MONTH				1	3
Eligibility Form		x			
History	x				
Signed Informed Consent[1]		x			
Complete Physical Exam	x			x[3]	
Signs and Symptoms/Eval.	x	x	x	x	x
Laboratory Evaluations					
OK-T4	x	x	x	x	x
OK-T8	x	x	x	x	x
NK Cell Activity	x	x	x	x	x
T11	x	x	x	x	x
PPD Skin Test		x		x	
CBC and Differential	x	x	x	x	x
Platelet Count	x	x			x
SMA 12 (4)	x	x	x	x	x
Concomitant Medication	x	x	x	x	x
Medication[2]		x		x	

1. Signed informed consent forms must have been acquired from each patient prior to enrollment (Day 0) into the study.
2. Medication is to be taken continuously throughout the treatment period (See Section 7.1).
3. If any clinical observations are abnormal at Day 28, then a complete physical examination will be performed at Day 90.
4. SMA 12 includes uric acid.

APPENDIX B

PATIENT INFORMED CONSENT FORM

PATIENT INFORMED CONSENT

Protocol Title: A Multi-Center, Randomized Double-Blind, Placebo-Controlled Study to Investigate the Effect of Isoprinosine® (inosine pranobex) in Volunteers with Uncomplicated Generalized Lymphadenopathy.

Participant's Name: _____ **ID#**_____

1. INTRODUCTION

Numerous studies over the past six years have demonstrated that Isoprinosine® has an effect on cells of the immune system.

A recently conducted study of 63 volunteers showed that Isoprinosine® improved certain immune functions which are related to immunodeficiency. Specifically, it was determined that administration of 3 grams per day of Isoprinosine® for 28 days resulted in significant improvement in the numbers of Natural Killer cells, total T-lymphocytes and Helper cells in volunteers. All of these cells are believed to play an important role in the regulation of the immune system.

2. PURPOSE OF STUDY

I understand that the purpose of this study is to determine the effect of Isoprinosine® upon the function of Natural Killer cells, the number of total T lymphocytes, and/or Helper cells among a group of volunteers presenting with signs and symptoms as described in the protocol.

I am being asked to participate in this study because there may be a moderate deficiency in one or more of my laboratory immune values. Such a deficiency may or may not be indicative of any illness or problems.

3. DESCRIPTION OF RESEARCH

a. <u>Study Medication</u>
I understand that this is a three-month, double-blind, placebo-controlled study. This means that I will be assigned by chance to one of two study groups using a randomization procedure.

1. One group of patients will receive 3 grams of Isoprinosine®, 6 tablets/day, for a 28 days.

2. Another group for controlled comparison will receive 6 tablets/day of placebo for 28 days. The placebo tablets are identical in appearance to the

drug tablets and are composed of an inert, harmless substance (lactose or milk sugar).

I understand that while I am taking the pills, my doctor will not know whether I am receiving placebo or drug.

b. Study Procedure and Schedule

Prior to receiving study medications, I understand that my written consent to participate in the study must be obtained and I will be given a routine physical examination and have blood tests performed at a screening visit. Should my immune tests be within the study requirements, I will be allowed to continue on the study and will be required to return for study visits on Day 0 (onset of study), and at 2 weeks, 4 weeks and 3 months.

I will receive a physical examination at the end of 1 month. A physical exam will also be conducted at 3 months if my doctor decides it to be necessary. I will be asked about any symptoms or signs that I may have experienced, as well as, any other medication I may have taken.

A sexual history will be obtained and maintained confidential.

Blood tests to study my immune system values will be done at the onset of the study and at week 2, week 4, then 2-months later. Sixty-five cc's of blood (aprox. two ounces) will be obtained from me each time.

c. The procedure described above involves the following possible risks and/or discomforts:

1. There may be a slight pain when the needle penetrates the skin of the arm.

2. A bruise may be left temporarily at the spot where the needle penetrates the skin of the arm.

3. There is a slight chance of inflammation of the vein.

d. Subjects undergoing treatments are advised to use barrier contraception during intercourse for the duration of the study and for three months after.

4. SIDE EFFECTS

This drug is metabolized to uric acid. In approximately 20% of the patients who take it, the drug may cause a transient rise in serum (blood) uric acid levels. Because of that, I

understand that not only my immune tests will be monitored, but also my uric acid levels.

In all prior instances where serum uric acid levels have risen, stopping drug treatment has resulted in the levels returning to normal. In any event, should it become necessary, I will be advised by my doctor if I am to discontinue the study medication.

Because Isoprinosine® is metabolized to uric acid, resulting in elevation of serum and urinary uric acid, Isoprinosine® should be used with caution in patients with a history of gout, urinary stones or kidney dysfunction.

5. POTENTIAL BENEFITS

The potential benefit to be derived from this treatment is a possible improvement in certain functions of my immune system. Also, the information gained from this study may be useful in developing treatment for certain immunodeficient disease states.

6. ALTERNATE TREATMENTS

This drug is investigational in the United States and at the present time, there is no known alternative treatment besides certain other experimental compounds currently in clinical testing.

7. UNDERSTANDING OF PARTICIPANTS

I have been given an opportunity to ask any questions concerning the investigational drug and the procedures involved in this study and my doctors have answered my questions. The investigational drug and procedures will be administered as described in this consent form. I hereby authorize Dr. _____, or the medical associates he may designate, to perform the designated procedures or dispense the investigational drug as described.

8. PARTICIPATION IS VOLUNTARY

I acknowledge that my participation is voluntary and I may withdraw from the study at any time without prejudice to my future medical care. Should I decide to withdraw from the study for any reason, I will contact Dr. _____ immediately, return all unused medication, and schedule an appointment for a follow-up examination at the earliest possible date. If it becomes necessary, the study may be terminated at any time by the investigator or study sponsor without my consent.

9. STUDY EXPENSE

There will be no expense to me for any tests or office visits directly involved in this study.

10. CONFIDENTIALLY

I have been assured that my confidentiality will be preserved and that names of patients will not be revealed in reports or publications resulting from this study without my expressed consent. The results of his study, however, may be made public without the inclusion of the names of any of the participants.

Qualified Monitors from Newport Pharmaceuticals International, Inc., and the Food and Drug Administration may, however, review, inspect, and copy records where appropriate and necessary.

11. ADDITIONAL PEOPLE TO CONTACT

If, during the course of this study, significant new information becomes available which may relate to my willingness to continue to participate, this information will be provided to me by the investigator.

If, at any time, I have questions regarding the research or my participation, I should contact Dr. _____ or _____ or Newport Pharmaceuticals International, Inc.'s Research Staff (714/642-7511) who will attempt to answer the questions.

If, at any time I have comments or complaints relating to the conduct of this research or if I feel I have suffered any research-related illness or injury, I may call _____, who represents the study participants to the Institutional Review Board, a committee whose purpose is to safeguard my rights and welfare while on the study.

12. COMPENSATION

I understand that if physical injury occurs as a direct consequence of taking the experimental medication, or the procedures required for administration of the medication, or the studies performed during the trial, the medical care required to treat the injury will be provided at no expense to me, providing that the cost of such medical care is not reimbursable through my own health insurance. However, no additional compensation for loss of income, pain and suffering or other form of compensation will be provided as a result of such injury or any subsequent medical care, including hospitalization.

FOR WOMEN

As with any experimental medication, it is essential that I do not become pregnant while on the study. I, therefore, assert that I am using adequate and safe contraception. If I have been receiving the drug, I will be advised not to attempt to become pregnant for one month after therapy.

13. CONSENT

Based upon the above, I consent to participate in the research and undergo the described procedures and have received a copy of the consent form.

Date	Signature of Participant
Witness	Signature of Person Responsible
Witness	Relationship

14. I have discussed this project with the participant (and/or his or her authorized representative) using a language which is understandable and appropriate. I believe that I have fully informed this patient of the nature of this study and its possible benefits and risks, and I believe the participant understood this explanation.

Physician/Investigator	Telephone Number	Date