DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date JUN 17 1997

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Mallinckrodt, Inc.
Albunex® - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA supplement.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Kimber C. Richter

Kimber C. Richter, M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved ✓ Disapproved _____ Date 6/17/97

Prepared by John C. Monahan, CDRH, HFZ-470, May 23, 1997, 594-1212

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[DOCKET NO. _____]

Mallinckrodt, Inc.; PREMARKET APPROVAL OF Albunex®

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the supplemental application by Mallinckrodt, Inc., St. Louis, MO, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of Albunex®. After reviewing the recommendation of the Radiological Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of June 17, 1997, of the approval of the supplemental application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Robert A. Phillips,
Center for Devices and Radiological Health (HFZ-470),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-594-1212.

SUPPLEMENTARY INFORMATION: On September 3, 1995, Mallinckrodt, Inc., St. Louis, MO 63134, submitted to CDRH a supplemental application for premarket approval of Albunex®. The device is an ultrasound contrast agent and is indicated for use with transvaginal ultrasound to assess fallopian tube patency.

On February 24, 1997, the Radiological Devices Panel of the Medical Devices Advisory Committe, an FDA advisory committee, reviewed and recommended approval of the supplemental application. On June 17, 1997, CDRH approved the supplemental application by a letter to the applicant from the Deputy Director of Clinical and Review Policy of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified

with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d))), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Jennifer Kettner, R.Ph.
Senior Regulatory Affairs Associate
Mallinckrodt Medical, Inc.
675 McDonnel Boulevard
P.O. Box 5840
St. Louis, Missouri 63134

JUN 17 1997

Re: P900059/S04
Albunex®
Filed: September 3, 1995
Amended: October 19, December 20, December 23, 1996, January 13, February 18, April 11, and May 20, 1997

Dear Ms. Kettner:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for Albunex®. This device is indicated for use with transvaginal ultrasound to assess fallopian tube patency. The PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 12 months when stored at 2^0 to 8^0C.

CDRH will publish a notice of its decision to approve your PMA supplement in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact John C. Monahan at (301) 594-1212.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name: Albumin (Human) 5%, Sonicated

Device trade name: ALBUNEX®

Applicant's Name: Mallinckrodt, Inc.
675 McDonnell Blvd.
St. Louis, MO 63134

PMA Holder's Name: Molecular Biosystems, Inc.
10030 Barnes Canyon Road
San Diego, CA 92121

PMA Number: P900059/Supplement 004

Date of Panel Recommendation: February 24, 1997

Date of Notice of Approval to the Applicant: JUN 17 1997

II. INDICATIONS FOR USE

ALBUNEX® is indicated for use with transvaginal ultrasound to assess fallopian tube patency.

III. DEVICE DESCRIPTION

ALBUNEX® is a suspension of air-filled albumin microspheres produced by sonication of Human Albumin, 5% Solution (albumin). The human albumin used to manufacture ALBUNEX® is U.S. Food and Drug Administration (FDA) licensed and is derived from plasma collected from donors who have been screened and tested according to the methods specified by the FDA.

These methods are designed to minimize the possibility that blood drawn from donors will contain communicable diseases or viruses such as hepatitis and HIV. The manufacturing process for Albumin Human, USP is designed to reduce the risk of viral transmission and includes heat treatment at 60°C for 10 hours. The following stabilizers are added per gram of albumin: 0.08 mmol sodium acetyl tryptophanate and 0.08 mmol sodium caprylate.

The protein in the ALBUNEX® microspheres makes up approximately 1% (w/w) of the total protein in the liquid, and the remaining 99% (w/w) is unchanged 5% human albumin. The solution contains 145±15 mEq/L of sodium, 100–130 mEq/L chloride, and potassium content not to exceed 2 mEq/L.

ALBUNEX® is a sterile, non-pyrogenic, clear amber liquid with an upper white layer containing the air-filled microspheres. Upon resuspension, the liquid becomes opaque (milky). The pH of ALBUNEX® is 6.4 to 7.4, which is the same as Albumin Human, USP. The concentration of microspheres is 3-5 x 10^8 per mL with a mean microsphere diameter range of 3.0 to 5.0 micrometers. The specification for microsphere size requires that 92.5% or more of the microspheres be less than 10 micrometers in diameter and that none exceed 32 micrometers in diameter.

ALBUNEX® is provided in single-use vials containing either 10 or 20 mL of a suspension of air-filled microspheres in 5% human albumin. For gynecologic use, ALBUNEX® is to be instilled into the uterus of the patient via a transvaginal catheter following the directions in the package insert. ALBUNEX® should be stored at 2° to 8°C and has 12 month expiration dating.

Dosage

Prior to administration, an appropriately sized, commercially available, flexible balloon catheter should be introduced into the uterus via the cervix, using sterile technique. The balloon should be inflated with sterile saline to seal the cervical canal. Sodium Chloride USP should be slowly instilled into the uterine cavity under ultrasound guidance. Up to 165 mL were used in clinical trials. The average volume of saline required ranges from 24 to 99 mL.

Following saline administration, ALBUNEX® may be slowly infused through the intrauterine catheter at a rate not to exceed 1 mL/sec. Transvaginal ultrasound imaging of the uterus, fallopian tubes, ovaries and pouch of Douglas should be performed before, during and following the administration. The usual first administration dose volume of ALBUNEX® is 7.2 mL, with an average range of 3.4 to 10 mL. Several administrations of ALBUNEX® may be given, up to a total dose volume of 30 mL.

Each administration of ALBUNEX® may be followed by a sterile saline flush to assist ALBUNEX® in flowing through the fallopian tubes. In clinical studies, saline flush volumes ranged from 1 to 90 mL and the most frequently used volume was 20 mL.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Precautions for this gynecological indication are listed below.

Always use sterile technique to insert the intrauterine catheter and remove it promptly following completion of the study to minimize the possible risk of infection.

Antibiotic prophylaxis should be considered in patients at increased risk of developing infection, such as those with a history of pelvic inflammatory disease. Patients with current gynecological infection should be treated with antibiotics and the procedure delayed until resolution of the infection.

Albunex® should be used with caution in patients with current abnormal uterine bleeding or with uterine anomalies which require acute surgical intervention.

Albunex® should not be used in patients with uterine anomalies that contraindicate the introduction of an intrauterine catheter.

Patients should be in the pre-ovulatory phase (the time immediately preceding ovulation) of their menstrual cycle.

Patient blood pressure and pulse rate should be monitored throughout the procedure. Intrauterine distention with sterile saline and Albunex® has been associated with a statistically significant changes from baseline in the systolic blood pressure and mean pulse rate. Two patients out of 178 (1.1%) experienced clinically significant decreases in vital signs. One of 178 (0.5%) patients experienced a clinically significant increase in systolic blood pressure.

Albunex® should be used only by individuals adequately trained in the use of transvaginal ultrasound and in the techniques of hysterosonosalpingography.

The following contraindication applies to Albunex® used for cardiographic and gynecologic indications:

ALBUNEX® should not be administered to patients with known or suspected hypersensitivity to blood, blood products or albumin.

The following warnings apply to Albunex® used for cardiographic and gynecologic indications:

The safety and effectiveness of ALBUNEX® have not been studied in children.

Inspect ALBUNEX® before resuspending:

DO NOT USE if the lower layer of liquid appears turbid or cloudy;
DO NOT USE if the upper white layer is absent;
DO NOT USE if the container has been damaged or the protective seal and/or rubber cap have been entered;
DO NOT USE if after resuspending ALBUNEX®, the product remains clear amber rather than appearing opaque and milky white.
DO NOT INFUSE ALBUNEX® into a patient at rates faster than 1 mL/sec.

Aspiration of blood back into the Albunex® containing syringe prior to intravenous administration is not recommended as this may promote the formation of clots

See attached labeling for general Warnings and Precautions not specifically intended for gynecological use.

V. ALTERNATIVE PRACTICES AND PROCEDURES

X-ray hysterosalpingography and diagnostic laparoscopy with chromopertubation (chromo-laparoscopy) are the standard clinical methods of evaluating fallopian tube patency. Hysterosonography, or saline-enhanced transvaginal ultrasonography is used primarily to assess the uterus, endometrium and ovaries; however, tubal patency may sometimes be inferred from this procedure.

VI. MARKETING HISTORY

In the United States ALBUNEX® received marketing authorization by the FDA in August 1994 for use in echocardiography, following intravenous injection, as an aid for ultrasound contrast enhancement of cardiac ventricular chambers and improvement of endocardial border definition in patients with suboptimal echocardiograms undergoing ventricular function and regional wall motion studies. For this indication, up to 0.30 mL/kg of ALBUNEX® is injected intravenously via a peripheral vein and a standard ultrasound imaging technique is applied to diagnose cardiac function. Since marketing authorization, approximately 27,000 units have been marketed in the United States and used in an estimated 17,000 patients.

The European Committee on Proprietary Medicinal Products (CPMP) issued an "approvable" opinion on ALBUNEX® on February 19, 1996 for the same echocardiodiagnostic indications approved in the United States. ALBUNEX® is trade named INFOSON® in Europe.

In Japan, ALBUNEX® was approved by the Ministry of Health and Welfare in October 1993 for similar echocardiographic indications, with more than 33,000 units marketed since approval. The device has not been withdrawn from any market for reasons of safety or effectiveness.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse device events following intravenous injection of ALBUNEX® are mild to moderate and of short duration. Rare life-threatening and fatal anaphylactic reactions have been associated with intravenous infusion of 5% Albumin Human, USP. Other reported adverse events included nausea, flushing, rash, headache, vomiting, chills and fever.

Three hundred nine women received transvaginal instillation of ALBUNEX® during the clinical trials. The most frequently reported adverse event associated with intrauterine instillation of ALBUNEX® to enhance transvaginal ultrasound examination was transient pelvic pain and cramping (12.2 %). Other adverse events reported were nausea (2.9%), vasovagal response (2.6%), dizziness (1.9%), vomiting (1.3%), abdominal pain (1.3%), back pain (0.6%), bleeding (0.6%), diarrhea (0.3%), flatulence (0.3%), urge to defecate

(tenesmus; 0.3%), tiredness (asthenia; 0.3%), fever (0.3%), headache (0.3%), hand numbness (hypesthesia; 0.3%), "bumps" on the soles of the feet (hyperesthesia; 0.3%), visual field defect (0.3%), myalgia (0.3%), perspiration (0.3%) and taste perversion (0.3%).

These adverse events were attributed to the procedure rather than ALBUNEX® in the clinical judgment of the investigators. This list includes adverse events experienced prior to ALBUNEX® administration, during the ultrasound procedure and for up to 24 hours following the ultrasound procedure. Most adverse events resolved spontaneously. Fourteen patients received mild analgesia in the form of acetaminophen, aspirin, ibuprofen or naproxen for cramping discomfort.

VIII. SUMMARY OF NONCLINICAL STUDIES

A. Microbiological Quality Control

All lots of ALBUNEX® are sampled and tested for sterility based on the Code of Federal Regulations title 21, section 610.12 and USP XXIII procedures for growth promotion of media, USP Sterility and Pyrogens. Media fills, personnel monitoring and environmental monitoring are performed as recommended in the FDA Guidelines for Aseptic Processing (June, 1987).

B. Nonclinical Effectiveness

Nonclinical effectiveness studies for this indication were not considered feasible.

C. Nonclinical Safety

The safety of ALBUNEX® for intrauterine instillation has been evaluated in the nonclinical studies which are summarized in Table 1.

TABLE 1. Summary of Nonclinical Safety Studies Conducted with ALBUNEX® in Experimental Animals.

Study	Species/strain and Number	Dose Group	Conclusions
Assessment of Potential Irritative Effects of Albunex in the Fallopian Tube and Uterus of Rabbits	New Zealand White Rabbits 3 3 3	Albunex Diatrizoate Meglumine Diatrizoate Sodium 37% iodine 0.9% Sodium Chloride	Instillation of Albunex® into the fallopian tube and uterus caused no treatment related changes in the ovaries, fallopian tubes or uteri. A single focal area of inflammation was observed in the skeletal muscle section in an Albunex® treated animal. The focal nature of the region suggested traumatic injury and not a compound related phenomena.
Assessment of Potential Irritative Effects of Albunex in the Peritoneal Cavity of the Female Rat	Sprague–Dawley Rats 12 12 12	Albunex Diatrizoate Meglumine Diatrizoate Sodium 37% iodine 0.9% sodium chloride	Intraperitoneal injection of Albunex® caused no gross or microscopic abnormalities in the peritoneal cavity or abdominal organs at 6 hrs, 24 hrs, or 7 days after administration.

The special toxicity testing conducted for this indication explored the potential irritation of the test material on the lumenal surfaces of the fallopian tube and uterus. The potential irritative effect of ALBUNEX® was also evaluated on the peritoneum and the surface of other abdominal organs. The irritative potential of ALBUNEX® was tested in Sprague–Dawley rats and New Zealand White Rabbits. These studies were performed in compliance with Good Laboratory Practice (GLP) regulations. The results of these studies demonstrate that ALBUNEX® causes no irritation or inflammation of the lumenal surfaces of the fallopian tube, uterus, ureter and urinary bladder. In addition, ALBUNEX® produces no inflammation of the peritoneal lining or the surfaces of other abdominal organs. The results of the individual nonclinical studies are summarized below.

1. Assessment of Potential Irritative Effects of ALBUNEX® in the Fallopian Tube and Uterus of Rabbits

This investigation assessed the potential irritative effects of ALBUNEX® instilled into the fallopian tube and uterus of rabbits. Under fluoroscopic guidance a sterile catheter system was positioned in the fallopian tube of an anesthetized rabbit via the vagina and uterus. ALBUNEX® (n=3), diatrizoate meglumine diatrizoate sodium 37% iodine w/v (n=3), or 0.9% sodium chloride (n=3) was randomly injected into one of the fallopian tubes and the uterus each animal. Test and control substances were injected into the fallopian tube at a dose-volume of 0.5 mL/kg using a catheter system. A second dose of the same test or control material was instilled into the uterus at a dose-volume of 1.0 mL/kg. After administration of the test or control substances, the animals were returned to their home cage. Forty-eight hours (n=2/group) or two weeks (n=1/group) after treatment, the rabbits were euthanized. The genital tracts of each animal were examined for gross abnormalities. The uteri, fallopian tubes, ovaries and surrounding tissues were collected and placed in 10% formalin.

Instillation of ALBUNEX® into the fallopian tube and uterus of rabbits induced no change in the normal histology of the genital tract or the surrounding tissues. Gross and histological inspection of the tissues demonstrated no treatment-related changes in the ovaries, fallopian tubes or uteri. A single incidence of focal inflammation was detected in one skeletal muscle section from an ALBUNEX-treated animal. The focal nature and shape of the region indicates that the inflammation resulted from traumatic injury rather than an ALBUNEX-related phenomenon. These data show that ALBUNEX® instilled into the fallopian tube and uterus causes no inflammation in, or around the organs of the genital tract.

2. Assessment of Potential Irritative Effects of ALBUNEX® in the Peritoneal Cavity of the Female Rat

This investigation assessed the potential irritative effects of ALBUNEX® injected into the peritoneal cavity of female Sprague-Dawley rats. ALBUNEX® (n=12), diatrizoate meglumine diatrizoate sodium 37% iodine w/v (n=12) or 0.9% sodium chloride (n=12) was injected intraperitoneally into each rat. Test and control articles were injected at dose-volumes of 3.0 mL/kg. Four animals from each treatment group were euthanized either 6 hours, 24 hours or 7 days after injection. An abdominal necropsy was performed on each animal after euthanasia. The surface of the abdominal organs and structures were examined for gross abnormalities and signs of inflammation. Tissue samples were collected and placed in 10% buffered formalin. Specimens included the stomach, liver, spleen, sections of the duodenum, jejunum and ileum, the pancreas, caecum, a section of large intestine, both kidneys, the urinary bladder, both ovaries, the uterus, mesentery and injection site. Tissue samples were submitted for histological examination. Injection of ALBUNEX® or 0.9% sodium chloride into the peritoneal cavity caused no gross or microscopic abnormalities in the peritoneal cavity

or abdominal organs at any post-injection time point. In contrast, administration of diatrizoate meglumine diatrizoate sodium 37% iodine w/v caused minimal to mild acute peritonitis in animals euthanized 6 or 24 hours after injection. Other noted histological findings appeared across treatment groups and were considered to be related to the injection procedure. These data indicate that a single injection of ALBUNEX® introduced into the peritoneal cavity causes no inflammation of the peritoneum or abdominal organs in female rats.

Nonclinical studies have shown that ALBUNEX® produces no adverse effects following instillation into the reproductive tract of female New Zealand white rabbits or intraperitoneal injection in Sprague-Dawley rats.

D. Additional Nonclinical Safety

Thirteen preclinical pharmacology or toxicology studies were performed for the original ALBUNEX® indication. They included acute and subacute toxicity, local tolerance, mutagenesis, teratology and immunology studies. The results of these studies were submitted as part of PMA P900059 and are summarized in Table 2. An additional study was performed to determine pharmacokinetics, biodistribution, and excretion of [I^{125}] Albunex following a single intraperitoneal administration in Sprague-Dawley Rats. This study demonstrated that five minutes post injection the Albunex derived radioactivity was widely distributed within the peritoneal cavity with detectable levels outside the cavity. Concentrations in blood, plasma, and most tissues reach their maximum concentration within 1 to three hours. At 72 hours the thyroid contained 337 μg equiv/g while blood and plasma contained 0.033 and 0.053 μ equiv/g respectively. The majority of the Albunex derived radioactivity was eliminated via renal mechanisms. Total recovery for the 72 hour group was 94% of the administered [I^{125}] Albunex derived radioactivity.

TABLE 2. Summary of Additional Nonclinical Safety Studies Conducted with ALBUNEX® in Experimental Animals.

Type of Study	Species	ALBUNEX® Dose(s)	Conclusions
Acute Toxicity			
Acute Toxicity (Intravenous)	Rat	1, 2, 3, 4 or 5 mL/kg	No toxicity LD_{50}> 5mL/kg
Acute Toxicity (Intra-arterial)	Dog	5 mL/kg	No treatment-related clinical, gross or histopathological changes. No toxicity.
Acute Dose Escalation for Cardiovascular Effects (Intravenous)	Dog	0.22, 1.0, 2.0, 5.0, 10.0 and 20.0 mL/kg	No adverse cardiovascular or pulmonary effects. No changes in selected clinical pathology parameters. No morphological alteration in selected tissues.
Sub-acute Toxicity			
Sub-acute Toxicity (Intravenous)	Monkey	0.42 and 0.83 mL/kg, 3 times per week for 3 weeks.	No toxicity after repeated doses that are 1.4 times and 2.8 times max. cumulative dose for humans.
Local Tolerance			
Local Irritation (Intramuscular)	Rabbit	0.5 mL or 1.0 mL	ALBUNEX® gave similar degrees of inflammation as distilled water and 5% human albumin controls.
Acute Irritation (Intravenous and Perivascular)	Rabbit	0.5 mL or 1.0 mL	Similar inflammation as 5% human albumin control.
Mutagenesis			
Mutagenesis Ames Test (in vitro)	*Salmonella typhimurium*	0.1 mL to 300 mL	Not mutagenic
Teratology			
Teratology (Intravenous)	Pregnant rat	0.6 mL and 1.2 mL per day; Rat: Day 7-17 of pregnancy.	No lethal, growth inhibitory or teratogenic effects on embryos or fetuses. No toxicity or death in treated rats. Spleen weights increased in dams given human albumin or ALBUNEX®
Teratology (Intravenous)	Pregnant rabbit	0.6 mL and 1.2 mL per day; Rabbit: Day 6-18 of pregnancy.	No lethal, growth inhibitory or teratogenic effects on embryos or fetuses. No toxicity or death in treated rabbits. Spleen weights increased in dams given human albumin or ALBUNEX®.
Immunology			
Skin sensitization (Intradermal and filter paper patch)	Guinea pig	0.5 mL of a 1:20 dilution of ALBUNEX® in saline.	Not a skin sensitizer in guinea pigs.
Biocompatibility (in vitro)	Sera from human, dog, rabbit, rat or primate	ALBUNEX® diluted and incubated in sera.	ALBUNEX® is miscible with sera from all species tested. No coagulation, or separation or precipitation were observed.
Immunology (Intraperitoneal and intra-dermal)	Guinea pig	0.2 mL ALBUNEX® 2 times per week for 2 weeks.	ALBUNEX® is immunogenic in guinea pigs. ALBUNEX® or HSA produces strong anaphylaxis.
Immunology (Intramuscular)	Monkey	0.2 mL ALBUNEX® 2 times per week for 2 weeks.	ALBUNEX® is non-immunogenic in monkeys

IX. SUMMARY OF CLINICAL STUDIES

A. Background

A total of 433 infertile women were evaluated under the direction of 17 investigators in 16 clinical studies between October 1991 and November 1995. This includes 309 patients who underwent contrast-enhanced transvaginal ultrasound examination with ALBUNEX® (309 patients who received ALBUNEX® and two patients who underwent ultrasound examination only but experienced adverse events). One hundred twenty-two patients underwent hysterosalpingography (HSG) or saline-enhanced transvaginal sonography and did not receive ALBUNEX®. The study plan included three Phase 2 trials (383, 415 and IAXU033a) and five Phase 3 trials (463, 475, AXU033b, AXU048 and AXU056).

Studies 383 and 415 were clinical feasibility studies designed to determine the safety and efficacy of ALBUNEX-enhanced transvaginal ultrasonography for assessing fallopian tube patency. Safety was assessed in terms of clinical signs and symptoms, including vital-sign changes and adverse events during and after the administration of ALBUNEX®. Efficacy was assessed by the ability of the ALBUNEX-enhanced study to detect fallopian tube patency compared to HSG. In addition, the ability to detect uterine and other reproductive system abnormalities during ALBUNEX-enhanced ultrasonography was compared to baseline ultrasonography and HSG.

Study IAXU033a was designed to evaluate the effect of various doses of ALBUNEX® in the uterus, fallopian tubes and peritoneal cavity of women scheduled to undergo hysterectomy and bilateral salpingectomy. Safety was assessed by vital sign changes during and after the administration of ALBUNEX® and by peritoneal biopsy and bacterial cultures of the fallopian tubes following hysterectomy and bilateral salpingectomy. The endometrium, tubal mucosa and peritoneal biopsy specimen were also evaluated for signs of local reactions. Efficacy was determined by detection of flow through the fallopian tubes.

The objectives of Studies 463 and 475 were to determine the safety, tolerance and efficacy of ALBUNEX-enhanced transvaginal ultrasound hysterosalpingosonography (HSS) for assessing fallopian tube patency in adult women. Safety was assessed in terms of clinical signs and symptoms, including vital sign changes and adverse events during and after the administration of ALBUNEX®. Tolerance was assessed by determining the relative incidence of discomfort produced when ALBUNEX® was administered compared to saline in the saline-enhanced ultrasound procedure, or iodinated contrast media used for x-ray HSG. Efficacy was assessed by comparing the ability of the ALBUNEX-enhanced procedure to detect fallopian tube patency with baseline and saline-enhanced ultrasound, HSG and diagnostic laparoscopy. In addition, the ability of ALBUNEX-enhanced ultrasound examinations to detect uterine

and other reproductive system abnormalities was compared to baseline and saline-enhanced ultrasonography, HSG and laparoscopy.

The objectives of Studies AXU033b and AXU048 were to determine the safety and efficacy of ALBUNEX-enhanced transvaginal ultrasound HSS for assessing fallopian tube patency in adult women. Safety was assessed by evaluation of adverse events experienced by women during and after the administration of ALBUNEX®. Efficacy was assessed by comparing the ability of the ALBUNEX-enhanced procedure to detect fallopian tube patency to that of x-ray HSG with diagnostic laparoscopy as a reference.

Study AXU056 was designed to determine the safety, tolerance and efficacy of ALBUNEX-enhanced transvaginal (HSS) for assessing fallopian tube patency in adult women. Safety was assessed by evaluation of adverse events experienced by women during and after the administration of ALBUNEX®. Tolerance was assessed by a comparison of the intensity of reported discomfort experienced by women undergoing HSS and HSG. Efficacy was assessed by comparing the ability of ALBUNEX-enhanced HSS to detect fallopian tube patency to that of saline-enhanced HSS with HSG as reference.

Table 3 lists the study sites and number of patients enrolled.

Table 3. Study Site Information

Phase	*Study*	*Site*	*Investigator(s)*	*Patients*
2	383	University of South Florida	Anna Parsons, M.D.	10
2	415	Outpatient Radiology Center	Amy Thurmond, M.D.	4
3	463	University of South Florida	Anna Parsons, M.D.	30
3	463	Ultrasound Institute of Baltimore	Roger Sanders, M.D.	7
3	463	Huntington Reproductive Center	Paulo Serafini, M.D.	30
3	463	Columbia Presbyterian Medical Center	Donna Sessions, M.D. Jodi Lerner, M.D.**	15
3	475	Long Beach Memorial Hospital	Bill Yee, M.D.	7
3	475	Western Pennsylvania Hospital	Marcela Bohm-Velez, M.D.	23
3	475	Vanderbilt Hospital	Jeanne Cullinan, M.D.	5
3	475	Reproductive Specialty Centre	Charles Koh, M.D. Grace Janik, M.D. **	27
3	475	Lutheran General Hospital	Douglas Rabin, M.D.	12
3	475	Conceptions Reproductive Associates	Ray L. Gottesfeld. M.D.	11
2	IAXU033a	University Hospital Uppsala, Sweden	Jan Holte, M.D., Ph.D.	7
3	AXU033b	University Hospital Uppsala, Sweden	Jan Holte, M.D., Ph.D. Carsten Rasmussen, M.D. Ph.D. ** Karin Wadin, M.D. **	100
3	AXU048	University of Gotheburg, Sahlgrenska Hospital, Sweden	Seth Granberg, M.D., Ph.D. Jane Thorburn, M.D. Ph.D. ** Annika Strandell. M.D. ** Mats Asztely, M.D. **	105***
3	AUX056	Hospital Tenon, France	J.M. Bigot, M.D.	43
		Hospital Huriez, France	Yann Robert, M.D.	

** Co-Investigator

*** Five "pilot" (practice) patients were enrolled in this study. They were not included in the analysis of efficacy.

Table 4 summarizes the study objectives and patient populations of each trial.

Table 4. Study Objectives and Patient Populations

PROTOCOL	OBJECTIVE(S)	PATIENT POPULATION(S)	NUMBER OF PATIENTS PER GROUP	NUMBER OF PATIENTS/ GROUP
383	Safety, Efficacy	Infertile women scheduled to undergo HSG	10	10 ALBUNEX®
415	Safety, Efficacy	Infertile women scheduled to undergo HSG	4	4 ALBUNEX®
IAXU033a	Safety, Efficacy	Women scheduled to undergo hysterectomy	7	7 ALBUNEX®
463	Safety, Efficacy, Tolerance	Infertile women scheduled to undergo HSG or laparoscopy	82	80[1] ALBUNEX®
475	Safety, Efficacy, Tolerance	Infertile women scheduled to undergo HSG or laparoscopy	85	84[2] ALBUNEX®
AXU033b and AXU048	Safety, Efficacy	Infertile women	205[3]	104[3] ALBUNEX® 101 HSG
AXU056	Safety, Efficacy, Tolerance	Infertile women scheduled to undergo HSG	43	22 ALBUNEX® 21 Saline
				433/311 (ALBUNEX®)

1. Two patients dropped out prior to receiving ALBUNEX®. Three additional patients did not undergo a comparison exam.
2. One patient dropped out prior to receiving ALBUNEX®. A significant protocol deviation occurred with one patient and five patients did not meet entry criteria. They were evaluated for safety, but not efficacy.
3. Five "pilot" (practice) patients are included in this group. They were evaluated for safety, but not efficacy.

The method of administering ALBUNEX® was similar in all of the studies. Patients received transcervical administrations of ALBUNEX® through a balloon catheter followed by saline flushes. The dose volumes administered during the Phase 2 and Phase 3 studies are summarized in Table 5.

In the eight protocols, single ALBUNEX® dose volumes ranged from 0.0 mL to 10.0 mL and cumulative ALBUNEX® dose volumes ranged from 0.0 mL to 30.0 mL. Saline flush volumes ranged from 0.0 mL to 90.0 mL and cumulative saline flush volumes ranged from 0.0 mL to 120.0 mL.

Table 5. ALBUNEX® DOSE VOLUME RANGE (mL).

Phase/Study Number		ALBUNEX® Single Dose	ALBUNEX® Cumulative Dose	Saline Flush Dose	Saline Flush Cumulative Dose
Phase 2/ 383 and 415	Range	0.5–10.0	4.0–24.0	0.0–28.0	0.0–53.0
	Mean	3.4	10.2	3.8	11.8
	Std.	1.7	5.1	6.8	19.4
Phase 2 IAXU033a	Range	0.5–9.0	5.0–18.0	0.0–18.0	0.0–35.0
	Mean	3.1	9.4	7.5	22.4
	Std.	2.0	4.3	4.4	13.3
Phase 3/ 463 and 475	Range	0.0–10.0	2.0–30.0	0.0–90.0	0.0–120.0
	Mean	6.3	10.6	7.5	13.0
	Std.	3.3	5.6	12.4	19.1
Phase 3/ AXU033b and AXU048	Range	0.0 or 4.0	0.0–20.0	0.0–10.0	0.0–20.0
	Mean	3.1	8.4	3.3	8.9
	Std.	1.2	3.5	2.0	4.5
Phase 3/ AXU056	Range	2.0 or 4.0	6.0–30.0	0.0–5.0	4.0–30.0
	Mean	3.2	15.3	3.5	16.3
	Std.	1.0	5.9	1.5	6.5
ALL	Range	0.0–10.0	0.0–30.0	0.0–90.0	0.0–120.0
	Mean	4.4	10.2	5.2	12.1
	Std.	2.8	5.2	8.3	15.2

B. Safety Evaluation

For Studies 383, 415, 463 and 475 safety was assessed in terms of clinical signs and symptoms, including vital–sign changes and adverse events during and after the administration of ALBUNEX®. For Study IAXU033a, safety was assessed by vital sign changes during and after the administration of ALBUNEX® and by peritoneal biopsy and bacterial cultures of the fallopian tubes following hysterectomy and bilateral salpingectomy. The endometrium, tubal mucosa and peritoneal biopsy specimen were also evaluated for signs of local reactions. For Studies AXU033b, AXU048 and AXU056, safety was assessed by the evaluation of adverse events experienced by women during and after the administration of ALBUNEX®.

For Studies 383 and 415, safety evaluations were performed immediately prior to and after each ALBUNEX® administration and at 5 and 30 minutes following the last ALBUNEX® administration. Adverse event monitoring was performed for 30 minutes following ALBUNEX® administration and at 24 hours following ALBUNEX® administration.

During Study IAXU033a, a physical and gynecological exam, including blood pressure and pulse rate, was performed prior to the ultrasound exam and at 2 hours after the last ALBUNEX–enhanced exam. In addition, the patients recorded their morning body temperature for 3 days following the procedure. The women were monitored

during the exam and for 2 hours following the ALBUNEX–enhanced exam. The patients recorded discomfort or adverse events for 3 days following the procedure. Following the contrast–enhanced ultrasound, the women underwent hysterectomy and bilateral salpingectomy. The peritoneum was biopsied, bacterial cultures of the fallopian tubes were performed and the endometrium, tubal mucosa and peritoneal biopsy specimen were evaluated for signs of local reactions.

For Studies 463 and 475, pulse rate, systolic and diastolic blood pressures were recorded immediately before the first ALBUNEX® administration, within 5 minutes after the last administration, and 60 minutes after the last administration. Body temperature was recorded immediately before the first ALBUNEX® administration and 60 minutes after the last ALBUNEX® administration. All patients were monitored for adverse device events during ALBUNEX® administration and at 1 and 24 hours after the last ALBUNEX® administration.

During Studies AXU033b, AXU048 and AXU056, patients were observed closely for adverse events during the ultrasound examination and for up to 30 minutes following the last ALBUNEX® administration. Vital signs were not monitored.

Table 6 summarizes safety parameters that were tested for the protocols.

Table 6. Safety Evaluation

STUDY NUMBER	SAFETY PARAMETER	BASE LINE	ON STUDY	POST STUDY	NUMBER OF PATIENTS
383	Adverse Events		X	X	10
	Vital Signs (Blood Pressure, Pulse Respiratory Rate)	X	X	X	
415	Adverse Events		X	X	4
	Vital Signs (Blood Pressure, Pulse Respiratory Rate)	X	X	X	
IAXU033a	Adverse Events		X	X	7
	Physical and Gynecological Exam	X		X	
	Vital Signs (Blood Pressure, Pulse Rate, Temperature)	X		X	
	Biopsy of the endometrium, tubal mucosa and peritoneum			X	
	Bacterial cultures of the fallopian tubes			X	
463	Adverse Events		X	X	80
	Vital Signs (Blood Pressure, Pulse Respiratory Rate, Temperature)	X	X	X	
475	Adverse Events		X	X	84
	Vital Signs (Blood Pressure, Pulse Respiratory Rate, Temperature)	X	X	X	
AXU033b/ AXU048	Adverse Events		X	X	205
AXU056	Adverse Events		X	X	43

C. Tolerance Evaluation

Tolerance was evaluated in Studies 463, 475 and AXU056. For Studies 463 and 475, the investigator performing the ALBUNEX–enhanced ultrasound examination and the physician performing the HSG examination recorded the highest level of discomfort the patient reported experiencing. Discomfort was rated on a four–point scale: 0 = no discomfort, 1 = mild discomfort, 2 = moderate discomfort, and 3 = severe discomfort.

For Study AXU056, patients were asked to record their perception of the examination on a visual analogue scale ranging from "no Discomfort" to "Extremely Painful." Any discomfort was then related to the procedure, the contrast agent or the flushing. All reports of discomfort were tabulated with adverse events and were reported in that category.

D. Efficacy Evaluation

The entry and exclusion criteria were similar for Studies 383, 415, 463, 475, AXU033b, AXU048 and AXU056. Adult women undergoing clinical evaluation for

infertility were eligible for enrollment. The women were either to have been in the pre-ovulatory phase of their menstrual cycle (Studies 383, 415, 463, 475, AXU048, AXU056) or were to have had a negative pregnancy test (AXU033b).

Study IAXU033a was primarily a safety study designed to evaluate the effect of various doses of ALBUNEX® in the uterus, fallopian tubes and peritoneal cavity of women. The entry criteria were different because the target population was women scheduled to undergo hysterectomy and bilateral salpingectomy. The exclusion criteria were similar to all of the other studies.

Women with a history of allergy to iodinated contrast agents, known or suspected hypersensitivity to blood products, pregnant women, postmenopausal women and women enrolled in other clinical trials were excluded. In addition, women with a gynecologic infection (Studies 383, 415, 463, 475, IAXU033a, AXU048, AXU056), with abnormal uterine bleeding or uterine abnormalities which required surgical intervention, within one year post-partum, who were nursing a baby (Studies 383, 415, 463, 475), with known or suspected hepatis B or HIV infection (Studies IAXU033a, AXU033b, AXU048, AXU056), or who had an HSG examination within 6 months before the exam date (Study AXU056), were excluded.

Informed consent was obtained from all patients.

E. Clinical Trial Results

1. Population Characteristics

a. Study Numbers 383 and 415

Fourteen (14) female patients were enrolled in the two U.S. Phase 2 studies, conducted at one site each. All patients underwent baseline, saline and ALBUNEX-enhanced ultrasound imaging and HSG examination. No patient was excluded from the evaluation of safety or efficacy.

b. Study Number AXU033a

Seven women were enrolled in this study. All seven patients received ALBUNEX-enhanced ultrasonography followed by hysterectomy, salpingectomy and peritoneal biopsy. All seven were evaluable for safety and efficacy.

c. Studies 463 and 475

A total of 167 female patients were enrolled in the two U.S. Phase 3, open-label, multicenter comparative studies conducted at ten sites. Three patients were enrolled and had a study number assigned, but did not receive ALBUNEX®. Data for these patients were not included in the database. Four patients did not undergo comparison examinations. Because these patients received ALBUNEX®, they were included in the evaluation of safety. Four patients were enrolled who retrospectively did not meet study entry criteria. Although these patients did not meet entry criteria, they received ALBUNEX®; therefore, their data were included in the safety evaluation.

One hundred sixty-four (164) patients underwent the baseline, saline-enhanced, and ALBUNEX-enhanced examinations; 143 underwent HSG; 25 underwent diagnostic laparoscopy; and 8 underwent both HSG and diagnostic laparoscopy.

d. Study Number AXU033b/AXU048 (Combined Study)

Two-hundred twenty-six women (226) with a history of infertility lasting at least 1 year were included in the trial at two sites in Sweden. Twenty-one (21) were withdrawn before the first examination, so demographic data were only registered for the 205 patients who came to the first examination for HSS (104 patients) or HSG (101 patients). Five pilot patients were enrolled per the protocol design. These five patients were not included in the analysis of efficacy. There was no significant difference between groups or centers regarding demographic or parity data. The initial gynecological examination revealed no abnormal findings in the HSG group, while 8 women in the HSS group had abnormal findings. These included three cases of hydrosalpinx, three cases of ovarian cysts, two cases with uterine myoma and one unspecified finding.

e. Study Number AXU056

Forty-three (43) women were included in this trial at two sites in France. They were randomized into two groups. One group (21 women) received saline-only ultrasound and one group (22 women) received ALBUNEX® and saline flushes with ultrasound examination. All received HSG. Due to protocol changes during the trial, only 23 women were included in the efficacy analysis. None of the differences between the centers in demographic characteristics are likely to influence the safety or efficacy results. There was no relevant

difference between the centers in patient parity. The gynecological examination performed before the diagnostic procedure revealed normal findings in all but one patient.

2. Demography

A total of 433 women were enrolled in the studies, 311 women received ALBUNEX® and were evaluable for safety; 185 were evaluable for tolerance; and 273 women were evaluable for efficacy. Of the 273 women evaluable for efficacy, a total of 109 women had laparoscopy comparison (23 women in the U.S. Phase 3 Studies 463 and 475 and 86 women in the Swedish Phase 3 Studies AXU033b and AXU048). Table 7 summarizes the demographic data for the U.S. and European Phase 2 and Phase 3 studies.

TABLE 7. DEMOGRAPHIC SUMMARY.

	U.S. Phase 2	European Phase 2	U.S. Phase 3	European Phase 3	European Phase 3	All
Age (years)						
Range	21.1–44.6	38.0–50.0	21.6–45.6	22.2–42.5	21.1–51.8	21.1–51.8
Mean	35.0	43.6	34.1	31.0	33.6	32.8
std.	5.7	5.0	5.1	4.3	6.2	5.3
Weight (kilograms)						
Range	49.1–93.6	50.0–70.0	44.5–122.7	46.0–92.0	47.0–98.0	44.5–122.7
Mean	66.9	61.4	68.7	63.5	63.3	65.5
Height (centimeters)						
Race						
White	13	7	120	205**	27	372
Black	1	0	22	0	14	37
Asian	0	0	5	0	2	7
Hispanic	0	0	16	0	0	16
Other*	0	0	1	0	0	1
Total Number of Patients	14	7	164	205	43	433

* One Jordanian is included in this group.

** Swedish studies. Data not collected. All patients are assumed to be white.

3. Safety Results

a. Vital Signs

There were no clinically significant changes in any vital sign parameters during Studies 383, 415, IAXU033a and AXU056. Vital signs were not monitored during Studies AXU033b and AXU048.

Data for systolic and diastolic blood pressures, and pulse rates prior to and 5 and 60 minutes following the last ALBUNEX® administration, and body temperature at baseline and 60 minutes following the last ALBUNEX® administration were recorded during Studies 463 and 475. The mean systolic blood pressure was 116.1 mmHg at baseline, 116.2 mmHg at five minutes post-injection and 113.6 at 60 minutes post-injection. The mean diastolic blood pressure was 73.0 mmHg at baseline, 72.7 mmHg at five minutes post-injection and 71.8 at 60 minutes post-injection. The mean pulse rate was 77.5 beats per minute at baseline, 74.6 beats per minute at five minutes post-injection and 74.6 beats per minute at 60 minutes post-injection. The mean body temperature was 98.2 ° F at baseline and 98.2° F at 60 minutes post-injection.

A statistically significant drop of 2.5 mmHg from baseline occurred in the mean systolic blood pressure at 60 minutes following ALBUNEX® administration. Statistically significant decreases in the mean pulse rate occurred at 5 minutes and 60 minutes following ALBUNEX® administration, decreasing by 2.9 beats per minute from baseline for each time point. Although these decreases were statistically significant, they were not clinically significant.

Three patients experienced clinically significant vital signs changes. One patient experienced a decreased pulse rate from 70 beats per minute at baseline to 58 and 50 beats per minute at five and 60 minutes, respectively, post ALBUNEX® administration. One patient experienced a decrease in both systolic and diastolic blood pressure from 110/70 mmHg to 90/40 mmHg, and a decrease in pulse rate from 100 to 60 beats per minute following ALBUNEX® administration. The third patient experienced an increase in blood pressure from 114/80 at baseline to 136/98 at five minutes post ALBUNEX® administration. The blood pressure returned to 112/76 within 60 minutes following ALBUNEX® administration. While these changes were clinically significant, they did not adversely impact the patients.

b. Histopathologic Assessment

Histopathologic assessment of the uterus, fallopian tubes and peritoneum was performed during Study IAXU033a. Eighteen to 38 (mean 24) days after the ALBUNEX–enhanced ultrasound, the women underwent hysterectomy and bilateral salpingectomy. The peritoneum was biopsied, bacterial cultures of the fallopian tubes were performed, and the endometrium, tubal mucosa and peritoneal biopsy specimen were evaluated for signs of local reactions. All bacterial cultures yielded negative results. Macroscopic and microscopic evaluation of all tissue samples did not reveal any reactions that suggested a locally irritating effect from ALBUNEX®.

c. Adverse Device Events

Of the 311 women evaluable for safety in these studies, 62 (19.9%) patients experienced 85 adverse events, including the two patients who experienced clinically significant decreases in vital signs parameters which were characterized as vasovagal reactions by the investigator. The events included pelvic pain and cramping (38), nausea (9), vasovagal response (8), dizziness (6), vomiting (4), back pain (2), abdominal pain (4), metrorrhagia (2), diarrhea (1), flatulence (1), urge to defecate (tenesmus; 1), tiredness (asthenia; 1), fever (1), headache (1), hand numbness (hypesthesia; 1), "bumps" on the soles of the feet (hyperesthesia; 1), visual field defect (1), myalgia (1), perspiration (1) and taste perversion (1).

These adverse events were attributed to the procedure rather than to ALBUNEX® in the clinical judgment of the investigators. This list includes adverse events experienced during the ultrasound procedure, including events which occurred prior to ALBUNEX® administration, and for up to 24 hours following the ultrasound procedure. Most adverse events resolved spontaneously. Fourteen (14) patients received mild analgesia in the form of acetaminophen, aspirin, ibuprofen or naproxen for cramping discomfort. The adverse events experienced by patients in these studies are very similar to the types of adverse events experienced by patients undergoing HSG exams.

Table 8 lists the number of patients experiencing adverse events in the clinical trials.

TABLE 8. NUMBER OF PATIENTS EXPERIENCING ADVERSE EVENTS DURING THE U.S. OR EUROPEAN CLINICAL TRIALS (N=311).

Adverse Event	Number of Patients Experiencing
Abdominal Discomfort	4 (1.3%)
Asthenia (Tiredness)	1 (0.3%)
Back Pain	2 (0.6%)
Bleeding (Metrorrhagia)	2 (0.6%)
Diarrhea	1 (0.3%)
Dizziness	6 (1.9%)
Fever	1 (0.3%)
Flatulence	1 (0.3%)
Hand Numbness (Hypesthesia)	1 (0.3%)
Headache	1 (0.3%)
Hyperesthesia	1 (0.3%)
Myalgia	1 (0.3%)
Nausea	9 (2.9%)
Pelvic Pain and Cramping	38 (12.2%)
Perspiration	1 (0.3%)
Taste Perversion	1 (0.3%)
Tenesmus (Urge to Defecate)	1 (0.3%)
Vasovagal Response	8 (2.6%)
Visual Field Defect	1 (0.3%)
Vomiting	4 (1.3%)

4. Tolerance

Tolerance was not assessed in the U.S. Phase 2 studies, the European Phase 2 study or the Swedish Phase 3 studies. For the U.S. Phase 3 studies, there was a significant difference in the overall level of discomfort associated with some of the procedures. There was significantly less overall discomfort during the baseline exam, when no catheter was used, than during the ALBUNEX–enhanced exam or HSG. There was significantly more overall discomfort with saline than with ALBUNEX®. There was no difference in the overall

discomfort experienced by women undergoing the ALBUNEX–enhanced exam and HSG.

There was also a difference in the level of discomfort experienced with ALBUNEX® administration as compared to saline and to x–ray contrast media administration. The data suggest that the level of discomfort patients experienced when ALBUNEX® was administered was significantly less than their discomfort with either iodinated contrast agents or with saline. The administration of ALBUNEX® is at least as well–tolerated by the patients as iodinated contrast agents.

Tolerance was also assessed during the European Phase 3 study, AXU056. Patients recorded their perception of the examination on a visual analogue scale ranging from "No Discomfort" to "Extremely Painful." Any discomfort was then related to the procedure, the contrast agent or the flushing. Several patients reported pain or discomfort during the examination which appeared to be due to the procedure. There were no significant differences in the occurrence of pain or discomfort between the patients receiving ALBUNEX®, saline–only or iodinated contrast. All reports of discomfort were tabulated with adverse events and were reported in that category.

5. Effectiveness Results

Study IAXU033a did not have a comparison procedure. The results demonstrated that for B mode ultrasound, doses below 2 mL tended to be inadequate to detect flow, doses from 2 to 4 mL gave varying results, and doses from 4 mL and higher were adequate to determine patency.

6. HSG Comparison Results

Studies 383 and 415 compared ALBUNEX–enhanced transvaginal ultrasound examination to HSG for determining fallopian tube patency. The two methods agreed in 79% of patients for the right fallopian tube and in 86% of patients for the left fallopian tube. On a total tube basis, there were 28 fallopian tubes examined with agreement in 23 of 28 tubes, for an overall agreement of 82%. On a per–patient basis, the ALBUNEX–enhanced exam was bilaterally concordant with the HSG exam in 10 of 14 (71%) of patients.

Study AXU056 compared either ALBUNEX–enhanced HSS or saline–enhanced HSS to HSG. ALBUNEX® provided a significantly higher number of correct diagnoses than saline (20 vs. 12) as compared with HSG.

Studies 463 and 475 compared ALBUNEX–enhanced transvaginal ultrasound examination to determine fallopian tube patency with HSG, laparoscopy or

both. HSG was the comparative examination used for 139 of 155 (89.7%) evaluable women. Twenty three (23) of 155 (14.8%) women had laparoscopy comparison. Seven (7) of 155 (4.5%) had both HSG and laparoscopy. ALBUNEX-enhanced examination and HSG agreed for 95 of 139 (68.3%) women who underwent both procedures.

When the ALBUNEX-enhanced study and the HSG procedure disagreed, it generally was because one or the other study indicated a one-sided tubal blockage. ALBUNEX® and HSG agreed that bilateral patency was present for 70 of 139 (51.5%) women. For 120 (86.3%) women, the ALBUNEX-enhanced examination demonstrated that unilateral or bilateral patency was present. On a per-tube basis, ALBUNEX® concurred with 183 of 218 (83.9%) fallopian tubes found patent by HSG and 31 of 53 (58.5%) found blocked. The overall per-tube agreement with HSG was 214 of 271 (79.0%).

7. Laparoscopy Comparison Results

Laparoscopy comparison was not included in Studies 383, 415, IAXU033a and AXU056. The results of those studies were not integrated with the results from the U.S. and Swedish Phase 3 trials (Studies 463, 475, AXU033b and AXU048).

A total of 109 women (23 women in the U.S. studies and 86 women in the Swedish studies) underwent both ALBUNEX-enhanced HSS and laparoscopy and were evaluable for efficacy. Since several women had only one tube evaluated, there are a total of 213 tubal assessments. Table 9 lists the results of the ALBUNEX-enhanced HSS study compared to laparoscopy.

TABLE 9. ALBUNEX-ENHANCED HSS ACCURACY VS LAPAROSCOPY; PER-TUBE RESULTS OF STUDIES 463, 475, AXU033b AND AXU048.

	Laparoscopy			
ALBUNEX®	**Patent**	**Obstructed**	**Uncertain**	**Total**
Patent	123 (Sweden) 34 (U.S.) 157 (Total)	9 (Sweden) 0 (U.S.) 9 (Total)	3 (Sweden) 0 (U.S.) 3 (Total)	169
Obstructed	2 (Sweden) 5 (U.S.) 7 (Total)	11 (Sweden) 5 (U.S.) 16 (Total)	0	23
Uncertain	14 (Sweden) 1 (U.S.) 15	5 (Sweden) 1 (U.S.) 6 (Total)	0	21
Total	179	31	3	213

When the study data were combined, the overall sensitivity was 157/179 (87.7%); the specificity was 16/31 (51.6%), and the accuracy was 173/213 (81.2%).

8. Additional Study Results

A comparison of the results of the baseline, saline-enhanced and ALBUNEX-enhanced ultrasound procedures, relative to HSG and laparoscopy, was performed for Studies 463 and 475. The differences between the procedures are significant. ALBUNEX-enhanced ultrasound was significantly superior to the baseline and saline-enhanced procedures for accurately delineating tubal status. Table 10 lists those results.

TABLE 10. PER-PATIENT COMPARISON OF ALBUNEX® TO BASELINE AND SALINE-ENHANCED ULTRASOUND: FALLOPIAN TUBE PATENCY VS HSG OR LAPAROSCOPY (N=155).

Comparison of Interest		Agreement (%) with HSG or Laparoscopy	McNemar Test	
			chi square	p
Baseline vs. ALBUNEX®	Baseline	0 (0.0%)	103.1	<0.001
	ALBUNEX®	105 (67.7%)		
Saline vs. ALBUNEX®	Saline	28 (18.1%)	75.0	<0.001
	ALBUNEX®	105 (67.7%)		

The U.S. Phase 3 studies, 463 and 475, were conducted on young women who were all in generally good health but differed by race. A subgroup analysis on the influence of race on efficacy was made. While the numbers are too small to be statistically meaningful, the data suggest that the sensitivity, specificity, overall accuracy and positive and negative predictive values of the ALBUNEX-enhanced procedure are similar for all races.

9. Other Studies

No other studies were performed for this indication.

10. Published Literature

In the PMA Supplement, the sponsor has submitted a number of clinical references and abstracts on ALBUNEX®.

IX. OVERALL CONCLUSIONS DRAWN FROM STUDIES

The Center for Devices and Radiological Health (CDRH) reviewed all submitted laboratory, animal, and clinical data. The clinical studies on 309 women demonstrate that ALBUNEX® when used with transvaginal ultrasound can assist the physician in a determination of fallopian tubal patency. The animal and clinical studies provide reasonable assurance that Albunex is a safe and effective contrast agent for its labeled indications. The use of ALBUNEX® may reduce the need for hysterosalpingography and diagnostic laparoscopy.

X. PANEL RECOMMENDATION

A meeting of the FDA Radiological Devices Panel occurred on February 24, 1997 to review the sponsor's submission, PMA P900059 Supplement 4, as amended. The Panel recommended that supplement 4 be approved with the following conditions:

1. Revision of the Gynecology Precautions section of the labeling to indicate, "Patients with current gynecological infection should be treated with antibiotics and the procedure delayed until resolution of the infection."

2. Revision of the Gynecology Precautions section of the labeling to include a statement indicating that use of this device should only be undertaken by individuals with adequate training in the use of transvaginal ultrasound and specifically hysterosalpingosonography.

The Panel also indicated that the FDA and the company work on the inclusion of a clinical data section in the labeling that includes a chart indicating the relative effectiveness of this procedure compared to hysterosalpingography and laparoscopy with chromopertubation. In addition, it suggested that a warning be added to the label specifically referencing the gynecological indication which states, "This device is designed to demonstrate tubal patency and a determination of tubal blockage should be confirmed with other diagnostic modalities (see Clinical Data Section)."

XI. CDRH Decision

CDRH concurred with the Radiological Devices Panel's recommendation of February 24, 1997 and issued a letter to Mallinckrodt Medical on March 20, 1997, advising that its PMA was approvable subject to the changes identified above as recommended by the Panel and required by FDA. In an amendment received by FDA on April 11, 1997, the applicant submitted the required information. FDA issued an approval order on June 17, 1997. The applicant's manufacturing facilities were inspected on March 13-15, 18-20 and 26, 1996 and were found to

be in compliance with the device Good Manufacturing Practice regulations.

There are no required additional studies or post market surveillance studies for ALBUNEX® for this indication.

XII. Approval Specifications

A copy of the package insert, the vial label and the label applied to the shipping carton are attached.

ALBUNEX®†

albumin (human) 5%, sonicated

DESCRIPTION

ALBUNEX® is produced by sonication of albumin (human), 5% Solution. The human albumin used to manufacture ALBUNEX is U.S. Food and Drug Administration (FDA) licensed and is derived from plasma collected from donors who have been previously screened and tested according to the methods specified by the FDA. The human albumin solution is held at 60°C for 10 hours. The following stabilizers are added per gram of albumin: 0.08 millimole sodium acetyl tryptophanate, and 0.08 millimole sodium caprylate.

The protein in the ALBUNEX microspheres makes up approximately 1% (w/w) of the total protein in the liquid, and the remaining 99% (w/w) is unchanged 5% human albumin.

ALBUNEX is a sterile, non-pyrogenic liquid. Prior to inversion it appears as a clear amber liquid with an upper white layer containing the air-filled microspheres. Upon resuspension, the liquid is opaque (milky).

PARAMETERS

pH	6.4 - 7.4
Microsphere concentration	3 - 5 x 10^8/mL
Microsphere diameter (mean)	3.0 - 5.0 µm
Size distribution	92.5% less than 10 µm
Maximum diameter	32 µm

Single unit dose. Contains no preservatives.

CLINICAL PHARMACOLOGY

No human pharmacokinetic studies have been performed with ALBUNEX. For animal pharmacology refer to the animal data section.

INDICATIONS AND USAGE

Echocardiography

ALBUNEX is intended as an aid for ultrasound contrast enhancement of ventricular chambers, and improves endocardial border definition in patients with suboptimal echoes undergoing ventricular function and regional wall motion studies.

Gynecology

ALBUNEX is indicated for use with transvaginal ultrasound to assess fallopian tube patency.

This device is designed to demonstrate tubal patency, and a determination of tubal blockage should be confirmed with other diagnostic modalities (see Clinical Data Section).

CONTRAINDICATIONS

ALBUNEX should not be administered to patients with known or suspected hypersensitivity to blood products.

WARNINGS

The safety and effectiveness of ALBUNEX have not been studied in children.

Inspect ALBUNEX before resuspending:

DO NOT USE if lower level of product is turbid or cloudy.

DO NOT USE is white upper level of product is absent.

DO NOT USE if the container has been damaged or protective seal and/or rubber cap have been entered.

DO NOT USE if after resuspending the ALBUNEX, the product remains clear amber instead of changing to milky white.

DO NOT INFUSE ALBUNEX into a patient at rates faster than 1 mL/sec.

Aspiration of blood back into the ALBUNEX containing syringe prior to administration is not recommended as this may promote the formation of clots.

PRECAUTIONS - GENERAL

ALBUNEX should be administered with caution to patients with confirmed or suspected severe liver disease or adult respiratory distress syndrome (ARDS). See Animal Toxicology section.

Diagnostic procedures that involve the use of ALBUNEX should be carried out under the direction of a licensed practitioner having a thorough knowledge of the procedure and the safe use of the product.

Hypersensitivity reactions should be anticipated whenever protein-containing materials such as ALBUNEX are used in humans. Epinephrine, antihistamines, and corticosteroids should be kept available for immediate treatment of the patient's symptoms.

ALBUNEX contains no bacteriostatic preservatives and should not be used for more than one patient. Discard unused product.

PRECAUTIONS - *Echocardiography*

As in all non-contrast echocardiography studies, ALBUNEX contrast echocardiography should be accompanied by ECG monitoring to detect and document changes in cardiac cycles and wave patterns.

Use an angiocatheter with a 20 gauge or larger needle, and a three-way stopcock. The catheter should be inserted into as large a vein as possible to avoid potential under-delivery of contrast agent to the heart chambers. Avoid the use of hand or wrist veins.

ALBUNEX administration should be followed immediately by flushing with Normal Saline for Injection, USP, or Dextrose (5%) in water, USP. It is advisable to maintain an open (TKO) intravenous line. The safety of other intravenous solutions has not been studied when used with an intravenous ALBUNEX injection.

ALBUNEX may not enhance endocardial borders in echocardiographic views in which there is a poor acoustic window.

PRECAUTIONS - *Gynecology*

Always use sterile technique to insert the intrauterine catheter and remove it promptly following completion of the study to minimize the possible risk of infection.

Antibiotic prophylaxis should be considered in patients at increased risk of developing infection, such as those with a history of pelvic inflammatory disease. Patients with current gynecological infection should be treated with antibiotics and the procedure delayed until resolution of the infection.

ALBUNEX should be used with caution in patients with current abnormal uterine bleeding or with uterine anomalies which require acute surgical intervention.

ALBUNEX should not be used in patients with uterine anomalies that contraindicate the introduction of an intrauterine catheter.

Patients should be in the pre-ovulatory phase (the time period immediately preceding ovulation) of their menstrual cycle.

Patient blood pressure and pulse rate should be monitored throughout the procedure. Intrauterine distention with sterile saline and ALBUNEX has been associated with a statistically significant drop from baseline in the systolic blood pressure and mean pulse rate. Two patients out of 178 (1.1%) experienced clinically significant decreases in vital signs. One of 178 (0.5%) patients experienced a clinically significant increase in systolic blood pressure.

ALBUNEX should be used only by individuals adequately trained in the use of transvaginal ultrasound and in the techniques of hysterosonosalpingography.

INFORMATION FOR PATIENTS

Patients receiving ALBUNEX:

1. Inform your physician if you may be pregnant or are nursing an infant.
2. Inform your physician if you ever have had an allergic or hypersensitivity reaction to blood or blood products.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate carcinogenesis, mutagenesis or impairment of fertility. An *in vitro* assay (Ames assay) was negative for mutagenesis.

PREGNANCY CATEGORY B - *Echocardiology*

Animal reproduction studies have been performed in rats and in rabbits at doses up to four times the maximum cumulative dose to humans and revealed no evidence of impaired fertility or harm to the fetus due to ALBUNEX. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALBUNEX should be given to a woman who may be pregnant only if the benefits to that patient outweigh the unknown risks to the fetus.

PREGNANCY CATEGORY C- *Gynecology*

There are no adequate animal or human studies that pertain to possible adverse fetal effects.

NURSING MOTHERS

It is not known whether ALBUNEX is excreted in human milk. Because many administered substances are excreted in human milk, caution should be exercised when ALBUNEX is to be administered to nursing women.

PEDIATRIC USE

Safety and effectiveness have not been established in children.

ADVERSE EVENTS - *General*

Since ALBUNEX is sterile when coming from the manufacturer, bacterial contamination with the risk of post-infusion septicemia can only occur if the container has been damaged or following puncture of the rubber cap (see WARNINGS).

Rare life-threatening and fatal anaphylactic reactions have been associated with the administration of human albumin products. Infusion of 5% human albumin has been associated with nausea, flushing, rash, headache, vomiting, chills and fever.

ADVERSE EVENTS - *Echocardiography*::

GREATER THAN 1%	LESS THAN 1%
- Transient altered taste	- Calming sensation
- Headache	- Chest discomfort*
- Dizziness	- Depression
- Palpitations	- Diarrhea
	- Diaphoresis
	- Dyspnea
	- Epigastric burning
	- Flashing lights
	- Flushing/warmth
	- Hand cramping
	- Hematoma (mild)
	- Hypoglycemia
	- Increased thirst
	- Injection site tingling/soreness
	- IV infiltration
	- Lightheadedness
	- Low mid-back discomfort
	- Malaise, fatigue
	- Muscular/body ache
	- Nausea
	- Numbness (hand/finger)
	- Rash/pruritus
	- Skin eruptions
	- Tachycardia
	- Transient blurred vision

*Reported in two patients with angina and reocclusion following PTCA

ADVERSE EVENTS - *Echocardiography*

The reported adverse events following the use of ALBUNEX in human clinical studies of 370 subjects have been mild to moderate, of short duration and have resolved without treatment. The most frequently reported adverse event associated with the administration of ALBUNEX was transient altered taste (4.3%). Other reported adverse events were post-administration headache (1.9%), dizziness (1.1%), and palpitations (1.1%). The remaining adverse events occurred in less than 1% of patients either coincidental to the injection or within 24 hours following the study.

ADVERSE EVENTS - *Gynecology*

Adverse events reported with the intrauterine administration of ALBUNEX for transvaginal ultrasound, or within 24 hours following instillation, have been attributed to the procedure or coincidence, rather than to ALBUNEX, and have usually resolved without treatment. The most frequently reported adverse event was pelvic pain and cramping (12.2%). Other reported events were nausea (2.9%), vasovagal response (2.6%), dizziness (1.9%), abdominal discomfort (1.3%), and vomiting (1.3%). The remaining adverse events occurred in less than 1% of patients.

ADVERSE EVENTS - *Gynecology*:

GREATER THAN 1%	LESS THAN 1%
- Pelvic pain, cramping	- Back pain
- Nausea	- Metrorrhagia
- Vasovagal response	- Asthenia
- Dizziness	- Diarrhea
- Abdominal discomfort	- Fever
- Vomiting	- Flatulence
	- Hypesthesia
	- Headache
	- Hyperesthesia
	- Myalgia
	- Perspiration
	- Transient altered taste
	- Tenesmus
	- Visual field defect

SAFE MEDICAL DEVICES ACT OF 1990 (SMDA) DEVICE USER REPORTS

As of November 28, 1991, device user facilities (*ie* hospitals, nursing homes, ambulatory surgical facilities and outpatient treatment facilities) are required to report incidents:

"that reasonably suggest that a medical device has caused or contributed to a death of a patient, or serious injury or serious illness of a patient."

Report **only** those deaths, serious injuries or serious illnesses which occur in your facility and for which it is probable that ALBUNEX may have caused or contributed to the event. Reports of deaths must be made to the Food and Drug Administration (FDA) and to Mallinckrodt Medical, Inc. by telephone at (888) 744-1414. Reports of serious injury and serious illness must be made to Mallinckrodt Medical, Inc. *Please use Test Form Part I (Form FDA 3375-TEST), which is available from FDA.*

Division of Surveillance Systems (HFZ-533)
Center for Devices and Radiological Health
Food and Drug Administration 1350 Piccard Drive
Rockville, MD 20850
TEL: (301) 594-2735

DOSAGE AND ADMINISTRATION

SPECIAL HANDLING PRECAUTIONS

Allow the vials to come to room temperature before use. Inspect all vials prior to injection.

DO NOT USE if the bottom layer appears cloudy or turbid before resuspension.

DO NOT USE if the white top layer is absent as this is indicative of destroyed microspheres and may result in poor or no echo contrast.

The ALBUNEX vial must be inverted and gently rotated for approximately three (3) minutes to completely resuspend the microspheres. *Failure to suspend the microspheres in this way may result in under-deliver of microspheres and inadequate contrast. If after resuspension, ALBUNEX appears clear amber instead of milky white, DO NOT USE.*

ALBUNEX microspheres are FRAGILE. Never shake or drop the vial. To avoid destroying the microspheres, follow these precautions after resuspension:

* ***ALWAYS VENT THE VIAL WITH A STERILE NEEDLE OR STERILE SPIKE BEFORE SLOWLY*** *withdrawing ALBUNEX suspension into the injection syringe using a vent spike such as Burron Medical Inc.'s Mini-Spike™ Dispensing Pin (DP-1000) or an 18 Gauge or larger gauge needle.*
* ***ALWAYS WITHDRAW OR INJECT*** *ALBUNEX no faster than 1 mL/sec.*
* *ALBUNEX must be infused at a rate* ***NOT TO EXCEED*** *1 mL/sec.*
* *The time from resuspension of the ALBUNEX microspheres to injection must not exceed one minute.*

Intravenous

Prior to administration, place a 20 G or larger angiocatheter needle in a large antecubital arm vein and attach a sterile three-way stopcock. Avoid use of hand or wrist veins. Start intravenous infusion of Normal Saline for Injection, USP or Dextrose (5%) in water, USP, at a "to keep open, or TKO" rate.

Left Heart Studies

For left heart studies, **the initial recommended dose is 0.08 mL/kg.** If left ventricular opacification is inadequate (*ie* if moderate to full ventricular opacification is not visualized), a second dose up to 0.22 mL/kg may be given. *The total procedural dose should not exceed 0.30 mL/kg.* For equivalent ALBUNEX doses in mL, see conversion chart.

Immediately after each injection, turn the stopcock to "wide open." The patient's infused arm may be raised until contrast appears in the left cardiac chambers. At such

cumulatively in the feces. At 24 hours post-injection, 2% of the injected radioactivity was measured in blood and less than 1% remained in each of the following organs: liver, spleen, kidney, and lung.

An acute intravenous limit study was performed in rats using doses up to 5 mL ALBUNEX per kg body weight or 16 times the maximum recommended cumulative dose to humans (0.3 mL/kg)(MRCD). No signs of toxicity or abnormalities in gross anatomy or histopathology were observed.

A subacute toxicity study in monkeys demonstrated that doses up to 2.8 times the maximum recommended cumulative dose to humans administered three times per week for three weeks was not toxic in any way.

In pigs, intravenous ALBUNEX caused pulmonary hypertension and systemic hypotension. Experimental evidence has revealed this mechanism to be the phagocytosis of ALBUNEX microspheres by pulmonary intravascular macrophages with subsequent release of thromboxane A2, a vasoconstrictor hormone. This phenomenon is believed to be species-specific in that it has been confirmed repeatedly in pigs using as little as one-tenth the recommended dose; thromboxane metabolite levels were found to be elevated in blood in pigs but not in humans given intravenous ALBUNEX compared to baseline levels; the adverse hemodynamic events in pigs have been blocked using cyclooxygenase pathway inhibitors; and marginated monocytic phagocytic cells have not been observed in normal human lung (1,2).

The significance of this finding for humans is unknown. However, evidence of lung phagocytic activity has been found in patients with severe liver disease undergoing liver-spleen scans (3 - 5). Although similar events have not been observed in humans studied in clinical trials, caution is urged in patients with severe liver disease or adult respiratory distress syndrome.

A safety study was performed in monkeys using doses up to 2.8 times the MRCD and did not produce any abnormal pulmonary hemodynamic effects, *i.e.*, ALBUNEX did not increase mean pulmonary arterial pressure, pulmonary arterial systolic or diastolic pressure.

Studies conducted in humans and primates showed ALBUNEX to be non-immunogenic.

Instilled into fallopian tubes and uterus of rabbits, undiluted ALBUNEX produced no changes in the normal histology of the uterus, fallopian tubes, ovaries, peritoneum or surrounding peritoneal tissues. No inflammation in or around the organs of the genital tract was induced.

After intraperitoneal injection into rats, undiluted ALBUNEX caused no gross or microscopic abnormalities or inflammation in or around the organs of the genital tract, peritoneal cavity or abdominal organs.

HOW SUPPLIED

ALBUNEX is available in a box of six single dose vials. Each vial contains 10 mL (Cat. No. 2703-10) or 20 mL (Cat. No. 2703-20).

CAUTION: FEDERAL U.S. LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

REFERENCES

1. Gehr, P. et al. The normal lung: Ultrastructure and morphometric estimation of diffusion capacity. Respir. Physiol. *32*: 121-140, 1978.
2. Zeltner, T.B., et al. The postnatal development and growth of the human lung: I. Morphometry. Respir. Physiol. *67*: 247-267, 1987.
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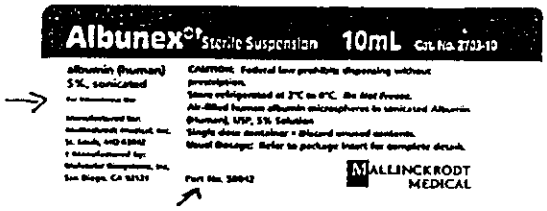
5. Garty, L., et al. Tc 99m colloid lung uptake in rare case of toxoplasmosis with liver involvement. Clin. Nucl. Med. *9*: 310-313, 1984.

Manufactured for:
Mallinckrodt Medical Inc., St. Louis, MO 63042

Manufactured by:
Molecular Biosystems, Inc., San Diego, CA 92121

Part No. 50047/R5 May 1997



Albunex©† Sterile Suspension 6 x 10 mL Cat. No. 2703-10

albumin (human)
5%, sonicated
For Intravenous Use

2703-10

CAUTION: Federal law prohibits dispensing without prescription.

Store refrigerated at 2°C to 8°C. *Do Not Freeze.*

Air-filled human albumin microspheres in sonicated Albumin (Human), USP, 5% Solution.

Albunex® microspheres are FRAGILE. Avoid destroying microspheres: Do NOT shake contents or drop bottle. Care must be used to VENT the bottle before SLOWLY drawing up the suspended dose.

Six (6) single dose containers. Discard unused contents.

Usual Dosage: Refer to package insert for complete details.

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St. Louis, MO 63042

Manufactured by: Molecular Biosystems, Inc.
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MEDICAL

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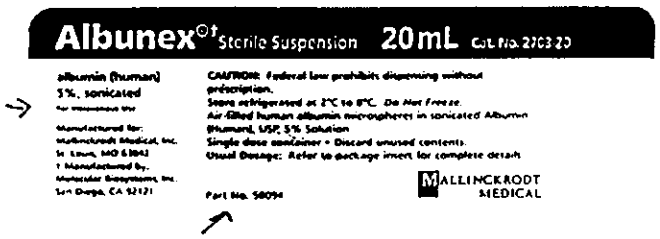
U.S. Patent No. 4,844,882
Part No. 50037

Current Labels



Albunex®† Sterile Suspension 6 x 20mL Cat. No. 2703-20

albumin (human)
5%, sonicated
For Intravenous Use

270320

CAUTION: Federal law prohibits dispensing without prescription.

Store refrigerated at 2°C to 8°C. *Do Not Freeze.*

Air-filled human albumin microspheres in sonicated Albumin (Human), USP, 5% Solution.

Albunex® microspheres are FRAGILE. Avoid destroying microspheres: Do NOT shake contents or drop bottle. Care must be used to VENT the bottle before SLOWLY drawing up the suspended dose.

Six (6) single dose containers. Discard unused contents.

Usual Dosage: Refer to package insert for complete details.

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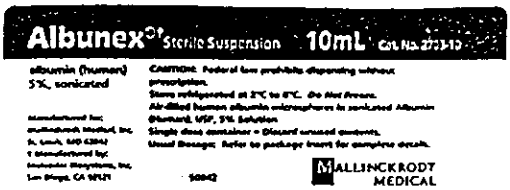
U.S. Patent No. 4,844,882
Part No. S0097

MALLINCKRODT MEDICAL

Current Labels



Albunex®† Sterile Suspension 6x10mL Cat. No. 2703-10

albumin (human)
5%, sonicated

CAUTION: Federal law prohibits dispensing without prescription.

Store refrigerated at 2°C to 8°C. *Do Not Freeze.*

Air-filled human albumin microspheres in sonicated Albumin (Human), USP, 5% Solution.

Albunex® microspheres are FRAGILE. Avoid destroying microspheres: Do NOT shake contents or drop bottle. Care must be used to VENT the bottle before SLOWLY drawing up the suspended dose.

2703-10

Six (6) single dose containers. Discard unused contents.

Usual Dosage: Refer to package insert for complete details.

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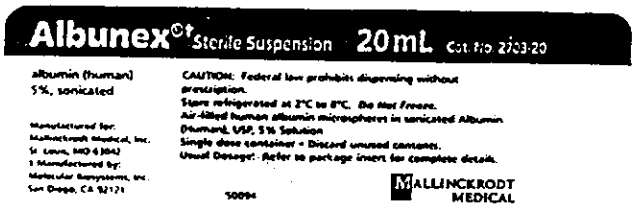
U.S. Patent No. 4,844,882
50037

MALLINCKRODT
MEDICAL

Proposed Revised Labels



Albunex®† Sterile Suspension 6 x 20mL Cat. No. 2703-20

albumin (human)
5%, sonicated

270320

CAUTION: Federal law prohibits dispensing without prescription.

Store refrigerated at 2°C to 8°C. *Do Not Freeze.*

Air-filled human albumin microspheres in sonicated Albumin (Human), USP, 5% Solution.

Albunex® microspheres are FRAGILE. Avoid destroying microspheres: Do NOT shake contents or drop bottle. Care must be used to VENT the bottle before SLOWLY drawing up the suspended dose.

Six (6) single dose containers. Discard unused contents.

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U.S. Patent No. 4,844,882
50097

MALLINCKRODT MEDICAL

Proposed Revised Labels