PRODUCT MONOGRAPH

ADRIAMYCIN* RDF*

(doxorubicin hydrochloride for Injection USP)

10 mg, 50 mg and 150 mg Vials

Antineoplastic agent

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Preparation:
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Control No. 086543

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NAME OF DRUG

ADRIAMYCIN* RDF*

Doxorubicin Hydrochloride for Injection USP

10 mg, 50 mg and 150 mg Vials

CAUTION:

ADRIAMYCIN (DOXORUBICIN HYDROCHLORIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPY DRUGS (SEE **WARNINGS** AND **PRECAUTIONS**). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. BECAUSE OF THE EXPERIENCE WITH CARDIAC TOXICITY, IT IS NOT RECOMMENDED TO EXCEED A TOTAL DOSE OF ADRIAMYCIN 550 MG/M^2 WITH THE 21 DAY REGIMEN AND 700 MG/M^2 WITH THE WEEKLY REGIMEN. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR WHO HAVE RECEIVED PRIOR ADRIAMYCIN CUMULATIVE DOSES EXCEEDING 400 MG/M^2 WITH THE 21 DAY REGIMEN AND 550 MG/M^2 UTILIZING THE WEEKLY REGIMEN.

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a wide spectrum of experimental tumours, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy of testes in rats and dogs.

Pharmacokinetic studies show that the intravenous administration of normal or radiolabelled ADRIAMYCIN (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. ADRIAMYCIN does not cross the blood brain barrier.

INDICATIONS AND CLINICAL USE

ADRIAMYCIN has been used successfully both as a single agent and also in combination with other approved cancer chemotherapeutic agents to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumour, neuroblastomas, soft tissue sarcomas, bone sarcomas, breast carcinomas, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, thyroid carcinoma, bladder carcinomas, squamous cell carcinoma of the head and neck, and gastric carcinoma.

ADRIAMYCIN has also been used by instillation into the bladder for the topical treatment of superficial bladder tumours.

A number of other solid tumours have also shown some responsiveness to ADRIAMYCIN alone or in combination with other drugs. (Refer to **DOSAGE AND ADMINISTRATION**) Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinomas, brain tumours and metastases to the central nervous system not to be significantly responsive to ADRIAMYCIN therapy.

CONTRAINDICATIONS

- Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones such as PHARMORUBICIN (epirubicin hydrochloride), daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- marked persistent myelosupression induced by prior treatment with other antitumor agents or by radiotherapy
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- history of severe cardiac disease
- previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones (See **WARNINGS** and **PRECAUTIONS)**

Intravesical use:

- invasive tumors that have penetrated the bladder wall
- urinary infections
- inflammation of the bladder

WARNINGS

Cardiac Function - Cardiotoxicity is a risk of anthracycline treatrment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/ or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, and atrioventricular and bundle-branch block have alsobeen reported. Those effects usually do not predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance and generally do not necessitate discontinuation of doxorubicin treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination; however, events occuring several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Subacute effects such as pericarditis/myocarditis also have been reported. Life-threatening CHF is the most severe form of anthracycline induced cardiomyopathy and is the cumulative dose-limiting toxicity of anthracycline drugs.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2, slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply. **IT IS RECOMMENDED NOT TO EXCEED**

A MAXIMUM CUMULATIVE DOSE OF 550 mg/m^2 of ADRIAMYCIN.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress cardiac contractility. Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. While cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present, it may be more likely to occur at lower cumulative doses in patients with these risk factors. The total dose of ADRIAMYCIN administered to a patient should take into account: prior or concomitant therapy with related compounds such as epirubicin and daunorubicin or anthracene derivatives; and/or radiotherapy to the mediastinal area.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after ADRIAMYCIN administration. (See **ADVERSE REACTIONS**)

Hematologic Toxicity

As with other cytotoxic agents, doxorubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death. Haematologic toxicity may require dose reduction or suspension or delay of ADRIAMYCIN therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage.

Secondary Leukemia

Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents. Secondary leukemia can have a 1 to 3 year latency period.

Hepatic Impairment

Doxorubicin is extensively metabolized by the liver and its major route of elimination is the hepatobiliary system. Toxicity to recommended doses of ADRIAMYCIN is enhanced by hepatic impairment, therefore, prior to the individual dosing and during treatment, evaluation

of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. Patients with elevated bilirubin may experience slower clearance of doxorubicin with an increase in overall toxicity. Lower doses of doxorubicin are recommended in these patients (See **DOSAGE AND ADMINISTRATION**). Patients with severe hepatic impairment should not receive doxorubicin (See **CONTRAINDICATIONS**).

Urological Effects

ADRIAMYCIN PFS may impart a red colouration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Gastrointestinal Events

Doxorubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of ADRIAMYCIN given by i.v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Vascular Effects

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see **DOSAGE AND ADMINISTRATION**).

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of doxorubicin.

Extravasation

Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately stopped.

Toxicites With Co-administration of Antineoplastic Agents

ADRIAMYCIN may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of

6-mercaptopurine have been reported. Radiation-induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of ADRIAMYCIN.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical Route of Administration

Administration of doxorubicin by the intravesical route may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., uretheral obstruction due to massive intravesical tumors.

Carcinogenesis & Mutagenesis, Impairment of Fertility

Doxorubicin was genotoxic in a battery of *in vitro* or *in vivo* tests. An increase in the incidence of mammary tumors was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

Pregnancy and Lactation

The embryotoxic potential of doxorubicin was confirmed *in vitro* and *in vivo*. When given to female rats before and during mating, pregnancy, and lactation, doxorubicin was toxic to both dams and fetuses.

Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If a woman receives doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be informed of the potential hazard to the fetus.

Doxorubicin is secreted into breast milk. Mothers should not breast-feed while undergoing chemotherapy with ADRIAMYCIN.

PRECAUTIONS

Initial treatment with ADRIAMYCIN RDF requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, ADRIAMYCIN RDF may induce hyperuricemia secondary to rapid lysis of neoplastic cells, particularly in patients with leukemia. The clinician should monitor the patient's serum chemistry and blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Hydration, urine alkalinization and allopurinol administration will help to prevent or minimize potential complications of tumor-lysis syndrome.

The systemic clearance of doxorubicin has been found to be reduced in obese patients (i.e., > 130% ideal body weight); see **DOSAGE AND ADMINISTRATION**, *Other Special Populations*).

ADRIAMYCIN RDF is not an anti-microbial agent.

Interactions

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see **WARNINGS** and **PRECAUTIONS**). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

ADVERSE REACTIONS

The following adverse events have been reported in association with doxorubicin therapy:

Cardiovascular:	sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, congestive heart failure *(*See **WARNINGS**)
Hematologic:	leukopenia, neutropenia, anemia, thrombocytopenia, hemorrhage
Gastrointestinal:	anorexia, nausea/vomiting, dehydration, mucositis/stomatitis, hyperpigmentation of the oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhea, colitis
Liver:	changes in transaminase levels, hyperuricemia
Endocrine:	amenorrhea, hot flashes, oligospermia, azoospermia
Ocular:	conjunctivitis/keratitis, lacrimation
Skin:	alopecia, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema
Vascular:	phlebitis, thrombophlebitis, thromboembolism
Urological:	red coloration of urine for 1 to 2 days after administration
Bladder, local:	pain, hemorrhage, and occasionally decreased bladder capacity upon instillation
Local:	severe cellulitis, vesication, tissue necrosis upon extravasation, erythematous streaking along the vein proximal to the site of the injection (see **DOSAGE AND ADMINISTRATION**)
Other:	anaphylaxis, infection, sepsis/septicemia, acute lymphocytic leukemia, acute myelogenous leukemia, malaise/asthenia, fever, chills, shock, cross sensitivity to lincomycin

OVERDOSAGE

Acute overdosage with ADRIAMYCIN RDF enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis. Acute overdosage with doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac alterations.

Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION

REFER TO GUIDELINES FOR SAFE PREPARATION AND HANDLING

Dosage

A variety of dose schedules has been used. The following recommendations are for use as a single agent only.

Intravenous (I.V.) Administration

The total doxorubicin dose per cycle may differ according to its use within a specific treatment regimen (e.g. given as a single agent or in combination with other cytotoxic drugs) and according to the indication.

The most commonly used dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21-day intervals. An alternative dose schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure. A dose of 30 mg/m^2 on each of three successive days repeated every 4 weeks has also been used.

Hepatic Dysfunction. ADRIAMYCIN dosage must be reduced if the bilirubin is elevated as follows: Serum Bilirubin 1.2-3.0 mg/dL -- give ½ of recommended starting dose, > 3 mg/dL -- give ¼ of recommended starting dose. Doxorubicin should not be administered to patients with severe hepatic impairment (See **CONTRAINDICATIONS**).

Other Special Populations. Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration. (See **WARNINGS, PRECAUTIONS**)

Intravesical Administration

When ADRIAMYCIN RDF is instilled intravesically for the treatment of superficial bladder carcinomas, the usual dose employed ranges from 50-80 mg in a total volume of 50-100 mL of 0.9% Sodium Chloride Solution USP with a contact time of 1-2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the ADRIAMYCIN solution. Instillation is repeated weekly for 4 weeks and subsequently at monthly intervals. Therapy may continue for one year or longer as no significant systemic toxicity has been reported. Care should be exercised in the handling and disposal of the voided urine. (Refer to **GUIDELINES FOR SAFE PREPARATION AND HANDLING**). PVC gloves should be worn and the urine should be inactivated by decolourizing it with 10 mL or more of sodium hypochlorite solution (household bleach).

Other methods of administration have been investigated including intra-arterial administration and also continuous or long term intravenous infusion utilizing appropriate infusion pumps.

Clinical studies support the efficacy of ADRIAMYCIN used concurrently with other chemotherapeutic agents. Listed below are tumour types and drugs used concurrently with ADRIAMYCIN:

Acute lymphocytic leukemia in adults: ADRIAMYCIN with vincristine and prednisone or with cytosine arabinoside, vincristine and prednisone.

Acute lymphocytic leukemia in children: ADRIAMYCIN with L-asparaginase, vincristine and prednisone.

Acute non-lymphocytic leukemia: ADRIAMYCIN with cytosine arabinosyl or with arabinosyl cytosine, vincristine and prednisone.

Carcinoma of the breast: ADRIAMYCIN with 5-fluorouracil and/or cyclophosphamide or with vincristine with or without cyclophosphamide.

Bronchogenic carcinoma, non-small cell: ADRIAMYCIN with cyclophosphamide, methotrexate and procarbazine or with cyclophosphamide and cisplatinum.

Bronchogenic carcinoma, small cell: ADRIAMYCIN with vincristine or etoposide (VP-16) and cyclophosphamide.

Hodgkin's disease: ADRIAMYCIN with bleomycin, vincristine and dacarbazine.

Non-Hodgkin's lymphoma: ADRIAMYCIN with cyclophosphamide, vincristine and prednisone, or bleomycin, cyclophosphamide, vincristine and prednisone.

Carcinoma of the ovary: ADRIAMYCIN with cisplatinum.

Soft tissue sarcoma: ADRIAMYCIN with dacarbazine, or with dacarbazine, cyclophosphamide and vincristine.

Carcinoma of the bladder: ADRIAMYCIN with methotrexate, vinblastine and cisplatinum or cisplatinum and cyclophosphamide or with 5-fluorouracil.

Carcinoma of the stomach: ADRIAMYCIN with 5-fluorouracil and mitomycin-C.

ADMINISTRATION:

Intravenous Administration

Care in the administration of ADRIAMYCIN RDF will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and

erythematous streaking. On intravenous administration of ADRIAMYCIN RDF, extravasation may occur with or without an accompanying stinging or burning sensation even if the blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

If it is known or suspected that subcutaneous extravasation has occurred, the following steps are recommended:

1. Attempt aspiration of the infiltrated ADRIAMYCIN solution.

2. Local intermittent application of ice for up to 3 days.

3. Elevation of the affected limb.

4. Close observation of the lesion.

5. Consultation with a plastic surgeon familiar with drug extravasations if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

ADRIAMYCIN RDF 10 mg, 50 mg and 150 mg vials should be reconstituted with 5 mL, 25 mL and 75 mL respectively of 0.9% Sodium Chloride Solution USP to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken until the contents are dissolved. A slight suspension may form which will completely dissolve on further shaking. The vials are under negative pressure and care should be taken to avoid a pressure build up. To minimize aerosol formation during reconstitution; particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution should also be avoided. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration 2-8^{o}C. The solution should be protected from exposure to direct light. For single dose vials, any unused solution should be discarded.

ADRIAMYCIN RDF should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Solution USP (0.9%) or 5% Dextrose Solution USP. The tubing should be attached to a Butterfly* needle, or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage, however, the dosage should be administered for not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A direct push injection is not

recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see **WARNINGS** and **PRECAUTIONS**).

Unless specific compatibility data are available, the mixing of ADRIAMYCIN solutions with other drugs is not recommended. Precipitation occurs with 5-fluorouracil and heparin.

Intravesical administration

Doxorubicin should be instilled using a catheter and retained intravesically for 1 to 2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the ADRIAMYCIN solution. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

GUIDELINES FOR SAFE PREPARATION AND HANDLING

Preparation and Handling

1. Personnel should be trained in good techniques for reconstitution and handling. Pregnant staff should be excluded from working with this drug.

2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surface should be protected by disposable, plastic-backed absorbent paper.

3. Personnel handling ADRIAMYCIN solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If ADRIAMYCIN contacts the skin or mucosa, the area should be washed with soap and water or sodium bicarbonate immediately. Do not abrade the skin by using a scrub brush and always wash hands after removing gloves.

4. In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes, proceed to a physician for a medical evaluation.

5. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

6. Directions for Dispensing from Pharmacy Bulk Vial

The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only.

Entry into the vial must be made with a sterile dispensing device such as the Econ-O-Set® Sterile Transfer System. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as increasing the potential for microbial and particulate contamination.

Swab the vial stopper with an antiseptic solution. Following carefully the manufacturer's instructions, insert the device into the vial. Withdraw contents of vial into syringes, using aseptic technique. Discard any unused portion within eight hours of initial entry.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with doxorubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000˚C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, ADRIAMYCIN may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the doxorubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Treat spilled powder or liquid with dilute sodium hypochlorite solution (1% available chlorine). Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

PHARMACEUTICAL INFORMATION

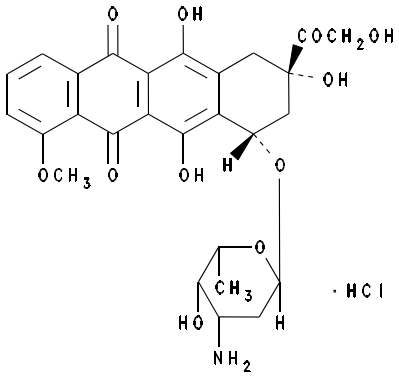
CHEMISTRY

Trade Name: ADRIAMYCIN* RDF*

Proper Name: Doxorubicin Hydrochloride

Chemical Name: (8S:10S)-10[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride (USAN).

Structural Formula:



Molecular Formula: $C_{27}H_{29}NO_{11}.HCl$

Molecular Weight: 579.98

Description: Doxorubicin hydrochloride is the hydrochloric acid salt of a glycoside antibiotic produced by *S. peucetius var. caesius*. It is a red-orange, almost odourless, hygroscopic powder, m.p. 205°C (dec.), $[\alpha]_D^{20}$ + 248°(c = 0.1 methanol), and soluble in water and dilute alcohols.

Composition:

ADRIAMYCIN RDF is a sterile, red-orange lyophilized powder. Methylparaben is added to enhance dissolution.

10 mg Vials	-	Each vial contains 10 mg of Doxorubicin Hydrochloride USP, 50 mg of lactose NF and 1 mg of methylparaben NF.
50 mg Vials	-	Each vial contains 50 mg of Doxorubicin Hydrochloride USP, 250 mg of lactose NF and 5 mg of methylparaben NF.
150 mg Pharmacy - Bulk Vial		Each vial contains 150 mg of Doxorubicin Hydrochloride USP, 750 mg of lactose NF and 15 mg of methylparaben NF.

Incompatibility:

Unless specific compatibility data are available, ADRIAMYCIN RDF should not be mixed with other drugs. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Doxorubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation. Precipitation also occurs with 5-fluorouracil.

RECONSTITUTION

Solutions for Reconstitution

0.9% Sodium Chloride Injection USP
(without bacteriostatic agent)

RECONSTITUTION TABLE

Vial Size	Diluent Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Concentration (mg/mL)
10 mg	5	5	2
50 mg	25	25	2
150 mg	57	75	2

See **Preparation of Solution** for instructions.

DOSAGE FORMS

Availability:

ADRIAMYCIN RDF (DOXORUBICIN HYDROCHLORIDE FOR INJECTION) is supplied as a sterile lyophilized powder. The following single dose vial sizes are available:

10 mg vials supplied in 10 vial cartons.

50 mg vials supplied in single vial cartons.

Pharmacy Bulk Vial:
150 mg vials supplied in single vial cartons.

NOTE:

THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM. THE PHARMACY BULK VIAL IS INTENDED FOR SINGLE PUNCTURE, MULTIPLE DISPENSING AND FOR INTRAVENOUS USE ONLY.

Entry into the vial must be made with a suitable, sterile transfer or dispensing device. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as it may increase the potential for microbial and particulate matter contamination.

In a suitable work area such as a laminar flow hood, swab the vial stopper with an antiseptic solution. Insert the device into the vial. Withdraw contents of the vial into sterile syringes using strict aseptic techniques. Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of the initial entry because of the potential for microbial contamination. Discard any unused portion. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature or 48 hours when refrigerated from the time of the initial entry into the Pharmacy Bulk Vial.

Storage:

Store ADRIAMYCIN RDF sterile lyophilized powder for injection at 15-30ºC and protected from light.

Stability of Solution

The reconstituted solution is stable for 24 hours at room temperature or for 48 hours under refrigeration. The solution should be protected from exposure to direct light and any unused solution should be discarded.

Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of initial entry because of the potential for microbial contamination.

PHARMACOLOGY

ADRIAMYCIN, when administered i.v., is rapidly cleared from the plasma of rodents, with concentration of the drug being seen in the liver, spleen, kidney, lung and heart. Drug excretion is prolonged and occurs predominantly via the liver.

In man, ADRIAMYCIN has also been shown to have a rapid plasma clearance and a large volume of distribution that suggests an extensive drug distribution into the tissues. Urinary excretion is minimal, with only 5% of the drug excreted during the first five days as measured by fluorimetric methods, suggesting prolonged tissue binding. After an injection of 1.5 mg/kg of tritium labelled ADRIAMYCIN approximately 50% of the administered radioactivity was detected in the feces in seven days, while in patients with impaired liver function, the fecal excretion accounted for only 20%. ADRIAMYCIN is metabolized predominantly by the liver to adriamycinol and several aglycone derivatives; approximately half of the drug excreted in bile was unchanged ADRIAMYCIN and 30% conjugates. Biliary excretion of ADRIAMYCIN was measured in one patient. A total of 40% of the administered dose was recovered as fluorescent material in the bile over a one week period.

The predominant fluorescent material in both urine and bile was ADRIAMYCIN followed by adriamycinol. Pharmacokinetic studies in patients with hepatic dysfunction show significant and prolonged plasma levels of ADRIAMYCIN metabolites associated with exaggerated clinical cytotoxicity. These observations are the basis of a requirement for dose de-escalation in patients with impaired hepatic function.

Neither ADRIAMYCIN nor any of its fluorescent metabolites were detectable in human cerebrospinal fluid obtained at varying intervals after drug administration in a variety of patients, including some with meningeal leukemia and cerebral metastasis, situations in which the blood brain barrier might be expected to be altered.

ANIMAL TOXICITY

Toxicology

The acute toxicity of ADRIAMYCIN in Swiss mice varies greatly according to the route of administration. The LD_{50} is 8.5 mg/kg by the intra-peritoneal route, 21.1 mg/kg by the intravenous route, and greater than 750 mg/kg by the oral route.

Chronic toxicity was studied in the rabbit and in the dog. ADRIAMYCIN when administered i.v. for three months at a daily dose of 0.125 mg/kg of body weight did not cause mortality or any measurable morphologic and functional changes in either species. At a dose of 0.25 mg/kg/day a few lesions were observed in the rabbit and more serious lesions in the dog, where the mortality rate reached 30%. The 0.5 mg/kg/day dose produced death in 40% of the treated rabbits within two months, and in 100% of the treated dogs within 10 days. Organs affected were gastrointestinal mucosa, hemopoietic tissues, and testes in both species, kidneys in the rabbit and skin (alopecia and melanosis) in the dog.

Teratology

ADRIAMYCIN when administered intravenously to rats at doses of 0.8 mg/kg/day during the period of organogenesis, resulted in an increased incidence of fetal resorption and fetal skeletal and soft tissue malformations. Rats treated intraperitoneally with doses of 1 mg/kg/day or greater also demonstrated skeletal and soft tissue malformations. The intravenous administration of ADRIAMYCIN to rabbits at doses of 0.1 mg/kg/day interfered with implantation and caused fetal resorption and at doses of 0.6 mg/kg/day was abortifacient. In addition, high single doses of 2 or 4 mg/kg in rabbits were shown to block implantation when administered on day 3 of pregnancy, to be embryotoxic when administered on day 7 of pregnancy, and to be abortifacient when administered on days 11, 15 or 20 of pregnancy.

Carcinogenicity

ADRIAMYCIN has been shown to be carcinogenic in the rat. The drug caused the appearance of breast fibroadenomas after a single i.v. dose of 8.0 mg/kg at an average of 33 weeks in 6 of 25 animals. Another animal developed a breast adenocarcinoma.

General

ADRIAMYCIN RDF was compared to the regular ADRIAMYCIN lyophilized formulation administered i.p. in P388 leukemic mice and i.v. to Gross leukemic mice. No difference in activity or toxicity was noted between the two formulations.

In local tolerance studies conducted in mice, rats, rabbits, and dogs, either by the intravenous or intradermal routes, the lesions induced by the ADRIAMYCIN RDF formulation appeared to be similar to those obtained with the ADRIAMYCIN lyophilized formulation.In other

tests using ADRIAMYCIN RDF, there was no evidence of incompatibility with human blood, plasma or serum.

REFERENCES

1. Zunino, F., *et al*: Interaction of Daunomycin and its Derivatives with DNA. Biochim. Biophys. Acta 277: 489-498, 1972.
2. Di Marco, A., *et al.*: Interaction of Some Daunomycin Derivatives with Deoxribonucleic Acid and Their Biological Activity. Biochem. Pharmacol. 20(6):1323-1328, 1971.
3. Di Marco, A.: Interactions of Oncostatic Agents with Molecular Mechanisms Involved in Transformation and Proliferation. Eur. Assoc. Cancer Res. 2nd Meet. (Heidelberg, Oct. 2-5, 1973).
4. Silvestrini, R., *et al*: Biological Activity of Adriamycin in vitro. Tumori 56(3): 137-148, 1970. (It. Eng. summary).
5. Wang, J.J. *et al.*: Comparative Biochemical Studies of Adriamycin and Daunomycin in Leukemic Cells. Cancer Res. 32:511-515, 1972.
6. Meriwether, W.D., and Bachur, N.R.: Inhibition of DNA and RNA Metabolism by Daunorubicin and Adriamycin in L1210 Mouse Leukemia. Cancer Res. 32:1137-1142, 1972.
7. Vig, B.K.; Chromosome Aberrations Induced in Human Leukocytes by the Antileukemic Antibiotic Adriamycin. Cancer Res. 31:32-38, 1971.
8. Duarte-Karim, M.: Affinity of Adriamycin to Phospholipids. A Possible Explanation for Cardiac Mitochondrial Lesions. Biochem. Biophys. Research Comm. 71:658-663, 1976.
9. Tritton, T.R. *et al.*: Adriamycin: A Proposal on the Specificity of Drug Action. Biochem. Biophys. Research Comm. 84:802-808, 1978.
10. Handa, K. and Sato, S.: Generation of Free Radicals of Quinone Group Containing Anticancer Chemicals in NADPH Microsome System as Evidenced by Initiation of Sulfite Oxidation. Gann. 66:43-47, 1975.
11. Bachur, N.R., *et al*: Anthracycline Antibiotic Augmentation of Microsomal Electron Transport and Free Radical Formation. Mol. Pharmacol. 13:901-910, 1977.
12. Doroshow, J.H., *et al*: Doxorubicin Toxicity: The Interaction of Drug and Endogenous Defenses against Free Radical Attack. Clin. Res. 26:434A, 1978.
13. Myers, C.E. *et al*: Adriamycin: The Role of Lipid Peroxidation in Cardiac Toxicity and Tumour Response. Science 197:165-176, 1977.
14. Blum, R.H., and Carter, S.K.: Adriamycin: A New Anticancer Drug with Significant Clinical Activity. Ann. Intern. Med. 80:249-259, 1974.
15. Tan, C., *et al*: Adriamycin Alone and in Combination in the Treatment of Childhood Neoplastic Disease. In, Ghione M., *et al* (eds.): Ergebnisse der Adriamycin Therapie. Adriamycin Symposium Frankfurt/Main, 1974. Berlin: Springer-Verlag, pp. 71-82, 1975.
16. Tan, C., *et al*: Adriamycin - An Antitumour Antibiotic in the Treatment of Neoplastic Diseases. Cancer 32(1):9-19, 1973.
17. Bonadonna, G., *et al*: Clinical Trials with Adriamycin - Results of Three Years Study. In, Carter, S.K., *et al* (eds): International Symposium on Adriamycin. New York: Springer-Verlag pp. 139-152, 1972.

18. Wang, J.J., *et al*: Therapeutic Effect and Toxicity of Adriamycin in Patients with Neoplastic Disease. Cancer 28(4):837-843, 1971.
19. Rozman, C., *et al*: Clinical Trials of Adriamycin. In, Carter, S.K., et al.(eds): International Symposium on Adriamycin. New York: Springer-Verlag, pp. 188-194, 1972.
20. Madon, E., *et al*: Adriamycin Use in Solid Tumours and in Lymphoblastic Leukemia of Children. In, Carter, S.K., et al. (eds): International Symposium on Adriamycin. New York: Springer-Verlag, pp. 234-235, 1972.
21. Middleman, E., *et al*: Clinical Trials with Adriamycin. Cancer 28(4): 844-850, 1971.
22. Frei, E., III, *et al*: Clinical Trials of Adriamycin. In, Carter, S.K., et al.(eds): International Symposium on Adriamycin. New York: Springer-Verlag, pp. 153-160, 1972.
23. Bonadonna, G., *et al* Evaluation of Adriamycin Alone and in Combination in Human Neoplasia. Int. Cong. Chemotherapy. Abstract 8 (Athens 8-14 Sep 1973). Vol. C (Abstr. B. VII-3).
24. O'Bryan, R.M., *et al*: Phase II Evaluation of Adriamycin in Human Neoplasia. Cancer 32:1-8, 1973.
25. Blum, R.H.: An Overview of Studies with Adriamycin in the United States. Cancer Chemotherapy. Rep. Pt. 3,6(2):247-251, Oct. 1975.
26. Fossati Bellani, F., *et al*: Adriamycin in Wilm's Tumour Previously treated with Chemotherapy. Eur. J. Cancer 11:593-595, 1975.
27. Benjamin, R.S., *et al*: Adriamycin Chemotherapy - Efficacy, Safety and Pharmacologic Basis of an Intermittent Single High Dosage Schedule. Cancer 33(1):19-27, 1974.
28. Gottlieb, J.A.: Adriamycin: Activity in Solid Tumours. In, Ghione, M., et al. (eds): Ergebnisse der Adriamycin Therapie. Adriamycin Symposium. Frankfurt/Main 1974. Berlin: Springer-Verlag. pp. 95-102, 1975.
29. Benjamin, R.S., *et al*: Adriamycin: A New Effective Agent in the Therapy of Disseminated Sarcomas. Med. Ped. Oncology. 1:63-76, 1975.
30. Oldham, R.K., and Pomeroy, T.C.: Treatment of Ewing's Sarcoma with Adriamycin (NSC-123127). Cancer Chemother. Rep. 56:635-639, 1972.
31. Savlov, E.D., *et al*: Study of Adriamycin vs. Cycloleucine in Treatment of Sarcomas. Am. Soc. Clin. Oncol. Proc. 10th Annu. Meet. (Houston, Mar. 27-30, 1974), vol. 15, p. 169, 1974 (Abstr. 738).
32. Rosenbaum, C., *et al*: Treatment of Advanced Soft Tissue Sarcoma. Proc. Amer. Assoc. Cancer Res. 18:287, 1977.
33. Gottlieb, J.A., *et al*: Adriamycin (NSC 123127) Used Alone and in Combination for Soft Tissue and Bony Sarcomas. Cancer Chemother. Rep. Part 3, Vol. 6:271-282, 1975.
34. Cortes, E.P., *et al*: Amputation and Adriamycin in Primary Osteosarcoma: A 5-Year Report. Cancer Treat. Rep. 62: 271-277, 1978.
35. Fossati Bellani, F., *et al*: Adjuvant Treatment with Adriamycin in Primary Operable Osteosarcoma. Cancer Treat. Rep. 62:279-281, 1978.
36. Hoogstraten, B., and George, S.: Adriamycin and Combination Chemotherapy in

Breast Cancer. Am. Assoc. Cancer Res. Proc. 65th Annu. Meet. (Houston, Mar. 27-30, 1974), Vol. 15, p.70, 1974 (Abstr. 279).
37. Gottlieb, J.A., *et al*: Superiority of Adriamycin over Oral Nitrosoureas in Patients with Advanced Breast Carcinoma. Cancer 33(3): 519-526, 1974.
38. Ahmann, D.I., *et al*: A Phase II Evaluation of Adriamycin (NSC-123127) as Treatment for Disseminated Breast Cancer. Am. Assoc. Cancer Res. Proc. 65th Annu. Meet. (Houston, Mar 27-30, 1974), Vol. 15, p.100, 1975. (Abstr. 397).
39. Rosner, K., et al.: Randomized Study of Adriamycin (ADM) vs. Combined herapy (FCP) vs. Adrenalectomy (ADX) in Breast Cancer. Am. Assoc. Cancer Res. Proc. 65th Annu. Meet. (Houston, Mar. 27-30, 1974). Vol. 15, p.63, 1974. (Abstr. 252).
40. Creech, R.H., *et al*: Low Versus High Dose Adriamycin Therapy of Metastatic Breast Cancer. Proc. Amer. Assoc. Cancer Res. 19:315, 1978.
41. Slavik, M.: Adriamycin Activity in Genitourinary and Gynecologic Malignancy. Cancer Chemother. Rep. Pt. 3,6(2):297-303, Oct. 1975.
42. Cortes, E.P., *et al* Adriamycin in Advanced Bronchogenic Carcinoma. Cancer 34:518-525, 1974.
43. Praga, C.: Co-operative Clinical Study on Adriamycin in Advanced Lung Tumours. In, Carter, S.K., *et al* (eds): International Symposium on Adriamycin. New York: Springer-Verlag, pp. 173-179, 1972.
44. Kenis, Y., *et al* : Results of a Clinical Trial with Intermittent Doses of Adriamycin in Lung Cancer. Eur. J. Cancer, 8:485-489, 1972.
45. Gottlieb, J.A., and Hill, C.S.: Chemotherapy of Thyroid Cancer with Adriamycin. N. Eng. J. Med. 290 4):193-197, 1974.
46. Sokal, M. and Harmer, C.L.: Chemotherapy for Anaplastic Carcinoma of the Thyroid. Clin. Oncol. 4:3-10. 1978.
47. Moertel, C.C. and Lavin, P.T.:Phase II-III Chemotherapy Studies in Advanced Gastric Cancer. Cancer Treat. Rep. 63:1863-1869, 1979.
48. The Gastrointestinal Tumour Study Group: Phase II-III Chemotherapy Studies in Advanced Gastric Cancer. Cancer Treat. Rep. 63:1871-1876, 1979.
49. Moertel, C.G.: Clinical Management of Advanced Gastrointestinal Cancer. Cancer 36:675-682, 1975.
50. Sallan, S.E., *et al* : Intermittent Combination Chemotherapy with Adriamycin for Childhood Acute Lymphoblastic Leukemia: Clinical Results. Blood 51:425-433, 1978.
51. Rodriguez, V., *et al* : Combination 6-mecaptopurine-Adriamycin in Refractory Adult Acute Leukemia. Clin. Pharmacol. Ther. 18(4):462-466, 1975.
52. Priesler, H.D., *et al* : Adriamycin-Cytosine Arabinoside Therapy for Adult Acute Myelocytic Leukemia. Cancer Treat. Rep. 61:89-92, 1977.
53. Starling, K.A., *et al* : Adriamycin, Vincristine, and Prednisone for Remission Induction in Children with Acute Nonlymphocytic Leukemia (ANLL) Proc. Amer. Assoc. Cancer. Res. 21:442, 1980.
54. Preisler, H., *et al* : Treatment of Acute Myelocytic Leukemia: Effects of Early Intensive Consolidation. Proc. Amer. Assoc. Cancer REs. 18:443, 1980.
55. McCredie, K.B.: Current Concepts in Acute Leukemia. Post. Grad. Med. 61:221-

224, 1977.
56. Elias, L., *et al* : Reinduction Therapy for Acute Leukemia with Adriamycin, Vincristine, and Prednisone: A Southwest Oncology Group Study. Cancer Treat. Rep. 63:1413-1415, 1979.
57. D'Angio, G.J., *et al* : Results of the Second National Wilm's Tumour Study (NWTS-2) Proc. Amer. Assoc. Cancer Res. 20:309, 1979.
58. Evans, A.E.,: Staging and Treatment of Neuroblastoma. Cancer 45:1799-1802, 1980.
59. Benjamin, R.S., *et al* : Advances in the Chemotherapy of Soft Tissue Sarcomas. Med. Clin. North Am. 61:1039-1043, 1977.
60. Antman, K., *et al* : Effective Adjuvant Chemotherapy for Localized Soft Tissue Sarcoma. Proc. Amer. Assoc. Cancer Res. 21:141, 1980.
61. Decker, D.A., *et al* : Preliminary Study of a Combination of Adriamycin, Bleomycin and Diammine dichloroplatinum in Advanced Cancer. Med. and Ped. Oncology 5:189-192, 1978.
62. Ultmann, J.E., *et al* : A "Broad Spectrum" Anticancer Agent Doxorubicin. Current Prescribing 8/28, pp. 68-72, 1978.
63. Gasparini, M., *et al* : Sequential Adjuvant Combination Chemotherapy in Ewing's Sarcoma. Proc. Amer. Assoc. Cancer Res. 19-:363, 1978.
64. Sutow, W.W., *et al* : Multidrug Adjuvant Chemotherapy for Osteosarcoma: Interim Report of the Southwest Oncology Group Studies. Cancer Treat. Rep. 62:289-294, 1978.
65. Ettinger, L.J., *et al* : Adriamycin (ADR) and Cis-Diammine dichloroplatinum (DPP) as Adjuvant Therapy in Osteosarcoma of the Extremities. Proc. Amer. Assoc. Cancer Res. 21:392, 1980.
66. Marcove, R., *et al*: Limb Salvage Resection and Chemotherapy (CT): Improved Survival and Function for Osteogenic Sarcoma (OSA) of the Proximal Humerus. Proc. Amer. Assoc. Cancer Res. 21:402, 1980.
67. Eilber, F.B., *et al* : Limb Salvage for Osteosarcoma. Proc. Amer. Assoc. Cancer Res., 20:330, 1979.
68. Jaffe, N., *et al*: High-dose Methotrexate in Osteogenic Sarcoma: A 5-Year Experience. Cancer Treat. Rep. 62:259-264, 1978.
69. Bull, J.M., *et al*: A Randomized Comparative Trial of Adriamycin Versus Methotrexate in Combination Drug Therapy. Cancer 41:1649-1657, 1978.
70. Smalley, R.V., *et al*: A Comparison of Cyclophosphamide, Adriamycin, 5-Fluorouracil (CAF) and Cyclophosphamide, Methotrexate, 5-Fluorouracil, Vincristine, Prednisone (CMFVP) in Patients with Metastatic Breast Cancer. Cancer 40:625-632,1977.
71. DeLena, M., *et al*: Adriamycin Plus Vincristine Compared to and Combined with Cyclophosphamide, Methotrexate, and 5-Fluorouracil for Advanced Breast Cancer. Cancer 35:1108-1115, 1975.
72. Hortobagyi, B.N., *et al*: Combination Chemotherapy of Ovarian Cancer with Cis-Diamminedichloroplatinum (CDDP), Adriamycin (Adr) and Cytoxan (CTX). Proc. Amer. Assoc. Cancer Res. 19:379, 1978.

73. Creech, R.H., *et al*: A Comparison of Standard Dose Adriamycin (SDH) and Low Dose Adriamycin (LDA) as Primary Chemotherapy for Metastatic Breast Cancer. Proc. Amer. Assoc. Cancer Res. 21:142, 1980.
74. Marcus, F., *et al*: 5FU + Oncovin + Adriamycin + Mitomycin-C (FOAM). An Effective New Therapy for Metastatic Breast Cancer Patients - Even Those Who have Failed CMF. Proc. Amer. Assoc. Cancer Res. 20:306, 1979.
75. Muss, H.B., *et al*: Adriamycin Versus Methotrexate in Five-Drug Combination Chemotherapy for Advanced Breast Cancer. Cancer 42:2141-2148, 1978.
76. Salmon, S.E. and Jones, S.E.: Studies of the Combination of Adriamycin and Cyclophosphamide (Alone or with Other Agents) for the Treatment of Breast Cancer. Oncology 36: 40-47, 1979.
77. Ehrlich, C.E., *et al.*: Combination Chemotherapy of Ovarian Cancer with Cis-Diamminedichloroplatinum (CDDP), Adriamycin (Adr) and Cytoxan (CTX). Proc. Amer. Assoc. Cancer Res. 19:379, 1978.
78. Turbow, M.M., *et al.*: Chemotherapy of Ovarian Cancer: Randomization between Melphalan and Adriamycin-Cyclophosphamide. Proc. Amer. Assoc. Cancer Res. 19:394, 1978.
79. Williams, C.J. and Whitehouse, J.M.A.: Combination Chemotherapy of Advanced Ovarian Carcinoma with Cis-Diammedichloroplatinum (DDC) Adriamycin and Cyclophosphamide (PACe). Proc. Amer. Assoc. Cancer Res. 21:136, 1980.
80. Turbow, M.M. *et al*: Chemotherapy of Ovarian Carcinoma: A Comparison of Melphalan vs. Adriamycin-Cyclophosphamide. Proc. Amer. Assoc. Cancer Res. 21:196, 1980.
81. Ehrlich, C.E., *et al.*: Response, "Second Look": Status and Survival in Stage III-IV Epithelial Ovarian Cancer Treated with Cis-Dichlorodiammine-platinum (IIK)(Cis-Platinum), Adriamycin (Adr) and Cyclophosphamide (CTX). Proc. Amer. Assoc. Cancer Res. 21:423, 1980.
82. Wallach, R.C., *et al.*: Chemotherapy of Recurrent Ovarian Cancer with Cis-Dichlorodiammine Platinum II and Adriamycin. Obstetr. and Gynec. 55:371-372, 1980.
83. Bruckner, H.W., *et al.*: Controlled Prospective Trial of Combination Chemotherapy with Cyclophosphamide, Adriamycin, and 5-Fluorouracil for the Treatment of Advanced Ovarian Cancer: A Preliminary Report. Cancer Treat. Rep. 63:297-299, 1979.
84. Livingston, R.B., *et al.*: Small-Cell Carcinoma of the Lung: Combination Chemotherapy and Radiation. Ann. Intern. Med. 88:194-199, 1978.
85. Chahanian, A.P., *et al.*: MACC (Methotrexate, Adriamycin, Cyclophosphamide, and CCNU) in Advanced Lung Cancer. Cancer 43:1590-1597, 1979.
86. Gralla, R.J., *et al.*: Cisdichlorodiammineplatinum II (DDP), Adriamycin and Cyclophosphamide Combination Chemotherapy in Advanced Non-Small Cell Bronchogenic Carcinoma. Proc. Amer. Assoc. Cancer Res. 19:353, 1978.
87. Mundia, A., *et al.*: Combination Chemotherapy in Non-Small Cell Lung Cancer. Proc. Amer. Assoc. Cancer Res. 17:107, 1976.
88. Bitran, J.D. *et al.*: Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine

(CAMP) - Effective Four-Drug Combination Chemotherapy for Metastatic Non-Oat Cell Bronchogenic Carcinoma. Cancer Treat. Rep. 60:1225-1230, 1979.
89. Cusumano, C.L., and Thar, T.C.: Aggressive Chemotherapy (CT) for Limited Stage Small Cell Bronchogenic Carcinoma (SCBC). Proc. Amer. Assoc. Cancer Res. 21:447, 1980.
90. Bitran, J., *et al.*: Cyclophosphamide, Adriamycin, and Cis-Platinum in the Treatment of Non-Small Cell Lung Cancer (SLC). Proc. Amer. Assoc. Cancer Res. 21:447, 1980.
91. Evans, W.K., *et al.*: Cyclophosphamide, Adriamycin, and Cis-Platinum in the Treatment of Non-Small Cell Lung Cancer (NSCLC). Proc. Amer. Assoc. Cancer Res. 21:447, 1980.
92. Cohen, J.M., *et al* : MACC in Advanced Lung Cancer (ALC): Reduction in Hematologic Toxicity without Compromising Effectiveness. Proc. Amer. Assoc. Cancer Res. 21:450, 1980.
93. Cohen, M.J., *et al*: Cyclic Alternating Combination Chemotherapy for Small Cell Bronchogenic Carcinoma. Cancer Treat. Rep. 63:163-170, 1979.
94. Greco, F.A.: Small Cell Lung Cancer. Complete Remission and Improved Survival. Am. J. Med. 66:625-630, 1979.
95. Einhorn, L.H., *et al*: Long Term Results in Combined-Modality Treatment of Small Cell Carcinoma of the Lung. Semin. Oncology 5:309-313, 1978.
96. Butler, T.P., *et al.*: 5-Fluorouracil, Adriamycin and Mitomycin-C (FAM), Chemotherapy for Adenocarcinoma of the Lung. Cancer 43:1183-1188, 1979.
97. Hyde, L., *et al*: Combined Chemotherapy for Squamous Cell Carcinoma of the Lung. Chest 23:603-607, 1978.
98. Santoro, A. *et al*: Non-Cross Resistant Regimens (MOPP and ABVD) vs. MOPP alone in Stage IV Hodgkin Disease (HD). Proc. Amer. Assoc. Cancer Res. 21:470, 1980.
99. Santoro, A., and Bonadonna, G.: Prolonged Disease-Free Survival in MOPP-Resistant Hodgkin's Disease After Treatment with Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD). Cancer Chemother. Pharmacol. 2:101-105, 1979.
100. Porzig, K.J., *et al.*: Treatment of Advanced Hodgkin's Disease with B-CAVe Following MOPP Failure. Cancer 41:1670-1675, 1980.
101. McKelvey, E.M.: Review of CHOP-HOP Combination Chemotherapy in Malignant Lymphoma. Proc. Amer. Assoc. Cancer Res. 19:415, 1978.
102. Canetta, R., *et al*: Sequential Non-Cross Resistant Regimens (CVP and ABP) in Advanced Non-Hodgkin Lymphomas (NHC). Proc. Amer. Assoc. Cancer Res. 21:189, 1980.
103. Laurence, J.C., *et al*: Six Drug (COP-BLAM) Combination Chemotherapy of Diffuse Histiocytic Lymphoma. Proc. Amer. Assoc. Cancer Res. 21:191, 1980.
104. Monfardini, S., *et al*: Cyclophosphamide, Vincristine, and Prednisone (CVP) Versus Adriamycin, Bleomycin and Prednisone (ABP) in Stage IV Non-Hodgkins Lymphomas. Med Pediatr Oncol. e:67-74, 1977.
105. Schein, P.S., *et al*: Bleomycin, Adriamycin, Cyclophosphamide, Vincristine and

Prednisone (BACOP) Combination Chemotherapy in the Treatment of Advanced Diffuse Histicytic Lymphoma. Ann. Inter. Med. 85:417-422, 1976.
106. Williams, S.D., *et al*: Chemotherapy of Bladder Cancer with Cis-Diamminedichloroplatinum (DDP) Adriamycin (Adr) and 5-Fluorouracil (5-FU). proc. Amer. Assoc. Cancer Res. 19:316, 1978.
107. Yagoda, A.: Chemotherapy of Metastatic Bladder Cancer. Cancer 45:1879-1888, 1980.
108. Sternberg, J.J., *et al.*: Combination Chemotherapy (CISCA) for Advanced Urinary Tract Carcinoma. JAMA 23:2282-2287, 1977.
109. Schein, P.S., *et al.*: The FAM (5-Flourouracil, Adriamycin, Mitomycin-C) and SMF (Streptozotocin, Mitomycin-C, 5-Flourouracil) Chemotherapy Regimens. In: Mitomycin-C. Current Status and New Developments. Schein PS ed, New York, Academic Press 1979, pp. 133-143.
110. Panattiere, F.J. and Heilbrun, L.: Experiences with Two Treatment Schedules in the Combination Chemotherapy of Advanced Gastric Carcinoma. In: Mitomycin C. Current Status and New Developments. Schein PS ed. New York, Academic Press 1979 pp. 145-157.
111. Bitran, J.D., *et al.*: Treatment of Metastatic Pancreatic and Gastric Adenocarcinomas with 5-Flourouracil, Adriamycin and Mitomycin C (FAM) Cancer Treat, Rep. 63:2041-2051, 1979.
112. Bunn, P.A., Jr., *et al*: 5-Flourouracil, Methyl CCNU, Adriamycin and Mitomycin C in the Treatment of Advanced Gastric Cancer. Cancer Treat. Rep. 62:1287-1293, 1978.
113. Levi, J.A., *et al.*: Improved Combination Chemotherapy in Advanced Gastric Cancer. Br Med J 2:1471-1473, 1979.
114. Woods, R.L., *et al.*: Metastatic Adenocarcinomas of Unknown Primary Site. N. Engl. J. Med. 303:87-89, 1980.
115. Valentine, J., *et al.*: Combination Chemotherapy for Adenocarcinoma of Unknown Primary Origin. Cancer Clin. Trials 2:265-268, 1979.
116. Davis, H.L.: Daunorubicin and Adriamycin in Cancer Treatment: An Analysis of Their Roles and Limitations. Cancer Treat Rep. 63:809-815, 1979.
117. Falkson, G., *et al*: Chemotherapy Studies in Primary Liver Cancer. Cancer 42:2149-2156, 1978.
118. Dewys, W.D., *et al*: Comparative Trial of Adriamycin and 5-Flourouracil in Advanced Prostatic Cancer-Progress Report. Cancer Treat Rep. 61:325-330, 1977.
119. Ihde, D., *et al.*: Effective Treatment of Hormonally Unresponsive Metastatic Carcinoma of the Prostate with Adriamycin and Cyclophosphamide. Cancer 45:1300-1310, 1980.
120. deTribolet, N., and Barrelet, L.: Successful Chemotherapy of Pinealoma. Lancet 2:1228-1229, 1977.
121. Drasin, H.: Treatment of Malignant Pheochromocytoma. West. Med. J. 128:106-111.1978.
122. Alberts, D.S., and Salmon, S.E.: Adriamycin (NSC-123127) in the Treatment of Alkylator-Resistant Multiple Myeloma: A Pilot Study. Cancer Chemother. Rep.

59:345-350, 1975.
123. Johnson, P.J., *et al.*: Induction of Remission in Hepatocellular Carcinoma with Doxorubicin. Lancet 1:1006-1009, 1978.
124. Bruckner, H.W. and Deppe, G.: Combination Chemotherapy of Advanced Endometrial Adenocarcinoma With Adriamycin, Cyclophosphamide, 5-Flourouracil and Medroxyprogesterone Acetate. Obstet. Gynec. 50:105-125, 1977.
125. Thigpen, J.T., *et al*: Phase II Trial of Adriamycin in the Treatment of Advanced or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study. Cancer Treat. Rep. 63:21-27, 1979.
126. Nathanson, L. and Kovacs, S.G.: Chemotherapeutic Response in Metastatic Medulloblastoma. Report of two cases and a review of the Literature. Med. Pediatr. Oncol. 4:105-110, 1978.
127. Legha, S.S., *et al* : Chemotherapy for Metastatic Carcinoid Tumours: Experiences with
32 Patients and a Review of the Literature. Cancer Treat. Rep. 61:1699-1703, 1977.
128. Camabareri, R.J., *et al*: FAM, 5-Flourouracil (F), Adriamycin (A) and Mitomycin-C(M) in Cholangiocarcinoma. Proc. Amer. Assoc. Cancer. REs. 21:419, 1980.
129. Scouros, M., *et al.*: Complete Remission (CR) in Chronic Lumphocytic Leukemia (CLL) Treated with Combination Chemotherapy. Proc. Amer. Assoc. Cancer Res. 21:441, 1980.
130. Odujinhin, O., *et al*: Clinical Experience with Adriamycin. Cancer Chemother. Rep. 37:95, 1973.
131. Minow, R.A., *et al.*: Adriamycin Cardiomyopathy: An Overview with Determination of Risk Factors. Cancer Chemother. Rep. Pt. 3, 6(2): 195-201, Oct. 1975.
132. Gilladoga, A., *et al*: The Cardiotoxicity of Adriamycin (NSC-123127) in Children. Cancer Chemother. Rep. Pt. 3, 6(2): 203-214, Oct. 1975.
133. Merrill, J., *et al*: Adriamycin and Radiation: Synergistic Cardiotoxicity. (Letter to the Editor). Ann. Intern. Med. 82(1): 122-123, Jan. 1975.
134. Denine, E.P., and Schmidt, L.H.: Adriamycin-induced Myopathies in the Rhesus Monkey with Emphasis on Cardiomyopathy. Sec. Toxicol. 14th Annu. Meet. (Williamsburg, Va, 9-13, Mar. 1975). Abstracts of Papers. p.81, 1975 (Abstr. 101).
135. LeFrak, E.A., *et al*: A Clinicopathologic Analysis of Adriamycin Cardiotoxicity. Cancer 32(2): 302-314, 1973.
136. Billingham, M., *et al*: Endomyocardial Biopsy Findings in Adriamycin Treated Patients. Am. Soc. Clin. Oncol. Proc. 12th Annu. Meet. (Toronto, Canada, May 4-5, 1976). Vol. 17, p. 281, 1976. (Abstr. C-180).
137. Jaenke, R.S.: Delayed and Progressive Myocardial Lesions After Adriamycin Administration in the Rabbit. Cancer Res. 36:2958-2966, Aug. 1976.
138. Cortes, E.P., *et al*: Adriamycin Cardiotoxicity - A Clinicopathological Correlation. Cancer Chemother. Rep., Pt. 2, 6(2):215-225, oct. 1975.
139. Minow, R.A., *et al*: QRS Voltage Change with Adriamycin Administration. Cancer Treat. Rep. 62(6):931-934, June 1978.
140. Carlon, G.C.: Prazosin in Acute Anthracycline Cardiomyopathy. Chest 77: 570-572,

1980.
141. Ewy, G.A., *et al*: Detection of Adriamycin Cardiotoxicity by Echocardiography. Ariz. Med. 35:402-405, 1978.
142. Balcerzak, S.P., *et al*: Systolic Time Intervals in Monitoring Adriamycin-induced Cardiotoxicity. Cancer Treat. Rep. 62:893-899, 1978.
143. Bloom, K.R., *et al.*: Echocardiographic Evaluation of Adriamycin Cardiotoxicity. Cancer 41:1265-1269, 1978.
144. Ramos, A., *et al* : Echocardiographic Evaluation of Adriamycin Cardiotoxicity in Children. Cancer Treat. Rep. 60:1281-1284, 1976.
145. Alexander, J. *et al*: Serial Assessment of Doxorubicin Cardiotoxicity with Quantitative Radionuclide Angiocardiography. N. Eng. J. Med. 300:278-283, 1979.
146. Billingham, M.E.: Anthracycline Cardiomyopathy Monitored by Morphologic Changes. Cancer Treat. Rep. 62:865-872, 1978.
147. Mason, J.W., *et al*: Invasive and Noninvasive Methods of Assessing Adriamycin Cardiotoxic Effects in Man: Superiority of Histopathologic Assessment Using Endomyocardial Biopsy. Cancer Treat. Rep. 62:857-864, 1978.
148. Bristow, M.R., *et al*: Doxorubicin Cardiomyopathy: Evaluation by Phonocardiography, Endomyocardial Biopsy and Cardiac Catheterization. Ann. Inter. Med. 88:168-175, 1975.
149. Wortman, J.E., *et al* : Sudden Death During Doxorubicin Administration. Cancer 44(5): 1588-1591, Nov. 1979.
150. Ershler, W.B., *et al* : Adriamycin Enhancement of Cyclophosphamide-induced Bladder Injury. J. Urol. 123:121-122, 1980.
151. Greco, F.A., et al.: Adriamycin and Enhanced Radiation Reaction in Normal Esophagus and Skin. Ann. Intern. Med. 85(3):294-298, 1976.
152. Mayer, E.G., *et al* : Complications of Irradiation Related to Apparent Drug Potentation by Adriamycin . Int. J. Rad. Oncol. Biol. Phys. 1:1179-1188, 1976.
153. Thompson, D.J., *et al*: Differential Sensitivity of the Rat and Rabbit to the Teratogenic and Embryo-Toxic Effects of Eleven Antineoplastic Drugs. Toxicol. Appl. Pharmacol. 45:353, 1978.
154. Casazza, A.M., *et al* : Tumours and Dental and Ocular Abnormalities After Treatment of Infant Rats with Adriamycin. Tumori. 63:331-338, 1977.
155. Data on File, Adria Laboratories, Columbus, Ohio.
156. Luce, J.K., *et al*: Prevention of Alopecia by Scalp Cooling of Patients Receiving Adriamycin. Cancer Chemother. Rep. 57:108, 1973.
157. Dean, J.C., *et al* : Prevention of Doxorubicin-induced Hair Loss with Scalp Hypothermia. N. Engl. J. Med. 301:1427-1429, 1979.
158. Barlock, A.L., *et al* : Nursing Management of Adriamycin Extravasation. Am. J. Nursing pp.95-96, Jan. 1979.
159. Zweig, T.I., and Kabakow, B.: An Apparently Effective Counter-measure for Doxorubicin Extravasation. JAMA 239:2116, 1978.
160. Rudolph, R., *et al* : Skin Ulcers Due to Adriamycin. Cancer 38: 1087-1094, Sept. 1976.
161. Reilly, J.J., *et al*: Clinical Course and Management of Accidental Adriamycin

Extravasation. Cancer 40:2053-2056, 1977.
162. Bowers, D.G. and Lynch, J.B.: Adriamycin Extravasation. Plastic Reconstruct. Surg. 61:86-92, 1978.
163. Rudolph, R.: Ulcers of the Hand and Wrist Caused by Doxorubicin Hydrochloride. Orthoped. Rev. 7:93-95, 1978.
164. Etcubanas, E., and Wilbur, Jr.: Uncommon Side Effects of Adriamycin (NSC-123127). Cancer Chemother. Rep. 58:757-758, 1974.
165. Donaldson, S.S., *et al* : Adriamycin Activating a Recall Phenomenon After Radiation Therapy. Ann. Intern. Med. 81(3):407-408, 1974.
166. Lenaz, L., and Page, J.A.: Cardiotoxicity of Adriamycin and Related Anthracyclines. Cancer Treat. Rep. 3:111-120, 1976.
167. Cortes, E.P., *et al* : Adriamycin Cardiotoxicity in Adults with Cancer. Clin. Res. 21:412, 1973.
168. Von Hoff, D.D., *et al* : Risk Factors for Doxorubicin-induced Congestive Heart Failure. Ann. Intern. Med. 91:710-717, 1979.
169. Praga, C., *et al* : Adriamycin Cardiotoxicity: A Survey of 1273 Patients. Cancer Treat. Rep. 63:827-834, 1979.
170. Rinehart, J. *et al* : Adriamycin Cardiotoxicity in Man. Ann. Intern. Med. 81:475-478. 1974.
171. Burg, J.R., *et al* : Evaluation of Cardiac Function during Adriamycin Therapy. J. Surg. Oncol. 6:519-529, 1974.
172. Hutchinson, R.J., *et al* : Systolic Time Intervals in Monitoring for Anthracycline Cardiomyopathy in Pediatric Patients. Cancer Treat. Rep. 62:907-910, 1978.
173. Benjamin, R.S., *et al* : An Endomyocardial Biopsy Study of Anthracycline-induced Cardiomyopathy; Detection, Reversibility and Potential Amelioration. Proc. Amer. Assoc. Cancer REs. 20:372, 1979.
174. Bristow, M.: Rational System for Cardiac Monitoring in Patients Receiving Anthracyclines. Amer. Assoc. Cancer Res. 21:356, 1980.
175. Billingham, M.E., *et al* : Anthracycline Cardiomyopathy Monitored by Morphologic Changes. Cancer Treat. Rep. 62:865-872, 1978.
176. Haskell, C.M., *et al* : Adriamycin (NSC-123127) by Arterial Infusion of Adriamycin in the Treatment of Cancer. Surg. Gynecol. Obstet. 144:335-338, 1977.
177. Kraybill, W.G., *et al* : Regional Intra-Arterial Infusion of Adriamycin in the Treatment of Cancer. Surg. Gynecol. Obstet. 144:335-338, 1977.
178. Garnick, M.B., *et al* : A Clinical Pharmacological Evaluation of Hepatic Artery Infusion
of Adriamycin. Cancer Res. 39:4105-4110, 1979.
179. Pavone-Macaluso, M., *et al* : Permeability of the Bladder Mucosa to Thiotepa, Adriamycin, and Daunorubicin in Men and Rabbits. Urological Res. 4:9-13, 1976.
180. Edsmyr, F., *et al* : Intravesical Therapy with Adriamycin in Patients with Superficial Bladder Tumours. In. Proc. First Conf. on Treatment of Urinary Tract Tumours with Adriamycin. Tokyo, May 12, 1979, Kyowa Hakko Kogyo Co. Ltd.
181. Banks, M.D., *et al* : Topical Instillation of Doxorubicin Hydrochloride in the Treatment of Recurring Superficial Transitional Cell Carcinoma of the Bladder. J.

Urol. 1118:757-760, 1977.
182. Yesair, D.W., *et al* : Pharmacokinetics and Metabolism of Adriamycin and Daunorubicin. In, Carter, S.K., *et al* (eds): International Symposium on Adriamycin. New York: Springer-Verlag, pp.117-123, 1972.
183. Di Fronzo, G., *et al* : Distribution and Metabolism of Adriamycin in Mice. Eur. J. Clin. Biol. Res. 16(6):572-576, 1971.
184. Di Fronzo, G., *et al* : Distribution and Excretion of Adriamycin in Man. Biomedicine 19:169-171, 1973.
185. Benjamin, R.S., *et al* : Pharmacokinetics and Metabolism of Adriamycin in Man. Clin. Pharmacol. Ther. 14:592-600, 1973.
186. Bachur, N.R., *et al* : Human Biliary Metabolites of Adriamycin (A) and Daunorubicin (D). Proc. Am. Assoc. Cancer Res. 14:14, 1973 (Abstr).
187. Benjamin, R.S., *et al* : Biliary Excretion of Adriamycin (A) in Man. Clinc. Res. 22:483A, 1974.
188. Bertazzoli, C., *et al* : Adriamycin: Toxicity Data, Experientia 26:389-390, 1970.
189. Bertazzoli, C., *et al* : Chronic Toxicity of Adriamycin: A New Antineoplastic Antibiotic. Toxicol. Appl. Pharmacol. 21:287-301, 1972.
190. Bertazzoli, C., *et al* : Different Incidence of Breast Carcinomas or Fibroadenomas in Daunorubicin or Adriamycin Treated Rats. Experienta 27:1209-1210, 1971.
191. Edsmyr, R., Andersson, L.: Chemotherapy in Bladder Cancer. Urological Res. 1978; 6:263-264.
192. Jacobi, G.H., Kurth, K.H., Klippel, K.F., *et al* : On the Biological Behaviour of T1-transitional Cell Tumours of the Urinary Bladder and Initial Results of the Prophylactic Use of Topical Adriamycin Under Controlled and Randomized Conditions. Edsmyr F. (ed.), Diagnostics and Treatment of Superficial Urinary Bladder Tumours. Radiumhemmut Karolinska Hospital, Stockholm: 83-94, Sept. 15, 1978.
193. Matsumura, Y., Ozaki, Y., Ohmori, H." Intravesical Instillation Therapy: Proc. First Conf. on Treatment of Urinary Tract Tumours with Adriamycin. Tokyo, May 12, 1979, Kyowa Hakko Kogyo Co. Ltd., 3-10.
194. Schulman, C.C.: Intravesical Chemotherapy for Superficial Bladder Tumours. In Denis, L., Smith, P.H., Pavone-Macaluso, M. (eds.) Clinical Bladder Cancer: 101-111, Plenum, New York, 1982.
195. Blinst Italian Co-Operative Group: Intravesical Doxorubicin for Prophylaxis of Superficial Bladder Tumours. Cancer: 54:756-761, 1984.
196. Horn, Y., Eidelman, A., Walach, N., *et al* : Intravesical Chemotherapy in a Controlled Trial with Thio-TEPA versus Doxorubicin Hydrochloride. J. Urol. 125:652-654, 1981.
197. Pavonne-Macaluso, M.: Intravesical Chemotherapy in the Treatment of Bladder Cancer. In Jones, S.E.: Current Concepts in the Use of Doxorubicin. Chemotherapy: 137-144, 1982.
198. Garnick, M., Schade, D., Israel, M., *et al* : Intravesical Adriamycin for Prophylaxis in the Management of Recurrent Superficial Bladder Cancer. J. Urol.: 53:585-587, 1983.

199. Kurth, H.H., Schroder, F.H., Tunn, V., *et al* : Adjuvant Chemotherapy of Superficial Transitional Cell Bladder Carcinoma: Preliminary Results of A European Organization for Research on Treatment of Cancer. Randomized Trial Comparing Doxorubicin Hydrochloride, Ethoglucid and Transitional Resection Alone. J. Urol.: 132:258-262, 1984.
200. Weiss, A., Metter, G., Fletcher, W., *et al* : Studies on Adriamycin Using a Weekly Regimen Demonstrating its Clinical Effectiveness and Lack of Cardiotoxicity. Cancer Treat. Rep. 60:813-822, 1976.
201. Weiss, A., Manthel, R.: Experience with the Use of Adriamycin in Combination with Other Anticancer Agents Using a Weekly Schedule with Particular Reference to Lack of Cardiac Toxicity. Cancer: 40:2046-2052, 1977.
202. Valdiviesio, M., Burgess, M., Ewer, M., *et al* : Adriamycin Given as a Weekly Schedule Without a Loading Course: Clinically Effective with Reduced Incidence of Cardiotoxicity. Cancer Treat. Rep. 64:47-51, 1980.
203. Chlebowski, R., Paroly, W., Pugh, R., *et al* : Adriamycin Given as a Weekly Schedule Without a Loading Course: Clinically Effective with Reduced Incidence of Cardiotoxocity. Cancer Treat Rep. 1980; 64:47-51.
204. Torti, F., Aston, D., Lum, B., *et al* : Weekly Doxorubicin in Endocrine-Refractory Carcinoma of the Prostate. J .Clin. Oncol. 1(8): 477-482, 1983.
205. Legha, S., Benjamin, R., Mackay, B., *et al* : Reduction of Doxorubicin Cardiotoxicity by Prolonged Continuous Infusion. Ann. Intern. Med. 96(2): 133-139, Feb. 1982.
206. Lokich, J., Bothe, A., Zipoli, T., Green, R., *et al* : Constant Infusion Schedule for Adriamycin: A Phase I-II Clinical Trial of a 30-Day Schedule by Ambulatory Pump Delivery System. J. Clin. Oncol. 1(1): 24-28, 1983.
207. Garnick, M., Weiss, G., Steele, G., *et al* : Clinical Evaluation of Long-Term, Continuous-Infusion Doxorubicin. Cancer Treat. Rep. 67(2): 1-10, 1983.
208. Legha, S., Benjamin, R., Mackay, B., *et al*: Adriamycin Therapy by Continuous Intravenous Infusion in Patients with Metastatic Breast Cancer. Cancer 49(9): 1762-1766, March, 1982.
209. Data on File. Adria Laboratories, Columbus, Ohio.
210. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. J Clin Oncol 1988;6(8):1321-1327.
211. Wang SQ. Electrocardiogram analysis of Adriamycin cardiotoxicity in 160 cases.Chin J Oncol 1991;13:71-73.
212. Jain D. Cardiotoxicity of doxorubicin and other anthracycline derivatives. J. Nucl. Cardiol. 2000; 7: 53-62.
213. Bielack SS, Erttmann R, Kempf-Bielack B, Winkler K. Impact of scheduling on toxicity and clinical efficacy of doxorubicin: what do we know in the mid-nineties? Eur J Cancer 1996;32A(10):1652-1660.
214. Lebwohl DE, Canetta R. New developments in chemotherapy of advanced breast cancer. Ann. Oncol. 1999; 10 (Suppl. 6): 139-46.
215. Kushner BH, Cheung NK, Kramer K, et al. Neuroblastoma and treatment-related myelodysplasia/leukemia: the Memorial Sloan-Kettering experience and a

literature review. J Clin Oncol 1998;16(12).
216.. Downing JR, Look AT. MLL fusion genes in the 11q23 acute leukemias. In: Molecular Genetics and Therapy of Leukemia, eds. EJ Freireich & H Kantarjian. Kluwer Acad., Norwell, Mass., 1996, pp. 73-92.
217. Mazué G, Williams GM, Iatropoulos MJ, et al. Anthracyclines: Review of genotoxicity and carcinogenicity studies. Int J Oncol 1996;8:525-536.
218. Mazué G, Iatropoulos M, Imondi A, et al. Anthracyclines: A review of general and special toxicity studies. Int J Oncol 1995;7:713-726.
219. Sutton R, Buzdar AU, Hortobagyi GNB. Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients. Cancer 1990;65:847-50.
220. Falkson G, Gelman RS, Torney DC, et al. The ECOG experience with cyclophosphamide, adriamycin, and 5-fluorouracil (CAF) in patients with metastatic breast cancer. Cancer 1985;56(2):219-24.
221. Da Cunha MF, Meistrich ML, Ried HL, et al. Active sperm production after cancer chemotherapy with doxorubicin. J Urol 1983;130(5):927-930.
222. Pryzant RM, Meistrich ML, Wilson G, et al. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 1993;11(2):239-247.
223. Bertazzoli C, Rallo F. Adriamycin - Effect on fertility and reproduction in female rats treated intravenously. Farmitalia Carlo Erba; 1977 Jun. Report No.DOXO/445i.
224. Bertazzoli C. Adriamycin - Teratological study in rats (intravenous administration) . Farmitalia Carlo Erba;1977 Sept. Report No. DOXO/446i.
225. Merei J, Hastorpe S, Farmer P, Hutson J.M. Visceral anomalies in prenatally adriamycin-exposed rat fetuses: A model for the VATER association. Pediatr Surg Int 1999;15:11-16.
226. Kotsios C, Merei J, Hutson JM, Graham HK. Skeletal anomalies in the adriamycin-exposed prenatal rat: A model for VATER association. J Orthop Res 1998;16(1):50-53.
227. Menegola E, Broccia ML, Prati M, et al. Comparative embryotoxicity of four anthracyclines: In vitro study on their effects on glutathione status. Toxicol In vitro 1997;11(1-2):33-41.
228. Bertazzoli C. Adriamycin?Teratological study in rabbits (i.v. administration) Farmitalia Carlo Erba;1977 Sept: Report No. DOXO/447i.
229. Artlich A, Moller J, Tschakaloff A, et al. Teratogenic effects in a case of maternal treatment for acute myelocytic leukemia-- neonatal and infantile course.Eur.J.Pediatr1994;153:488-91.
230. Galassi A, Hubbard SM, Alexander HR, Steinhaus E. Chemotherapy administration: practical guidelines. In: Cancer Chemotherapy ansd Biotherapy, 2nd Edition, eds. Chabner BA and Longo DL. Lippincott-Raven, Philadelphia, Pa. pp. 529-51, 1996.
231. AHFS Drug Information. Antineoplastic agents - doxorubicin hydrochloride. 2000, pp 913.
232. Dorr RT, Alberts DS. Pharmacology of doxorubicin. In Current Concepts in the

Use of Doxorubicin Chemotherapy. ed SE Jones, 1982.