Appendix B: Proposed Package Insert for Combidex

Combidex® (ferumoxtran-10)

DESCRIPTION

Combidex® (ferumoxtran-10), injection powder, lyophilized for solution, is a superparamagnetic iron oxide covered with low molecular weight dextran for intravenous administration as a magnetic resonance imaging (MRI) contrast media. Chemically, ferumoxtran-10 is a non-stoichiometric magnetite. The average particle size is less than 50 nanometers. Each vial of Combidex contains 210 milligrams of iron, 631 milligrams of dextran and 27 milligrams of sodium citrate. Following reconstitution with saline, the osmolality is approximately 365 mOsm/kg.

Average chemical formula: $FeO_{1.45}$ $[H(C_6H_{10}O_5)_n$ OH]

CLINICAL PHARMACOLOGY

General: Combidex is an intravenously injected colloidal superparamagnetic iron oxide coated with dextran. Superparamagnetic iron oxide contrast agents contain iron, an essential mineral. Combidex is endocytosed and metabolized by cells of the reticuloendothelial system (RES); the iron is incorporated into the normal metabolic iron pool.

Pharmacokinetics:

Pharmacokinetic data from both nonclinical and clinical studies of Combidex are consistent with a three phase model of initial vascular distribution of the iron oxide followed by phagocytosis or ingestion of the material primarily by the reticuloendothelial cells of the liver and spleen, with lesser amounts taken up by the macrophages of the lymph nodes. After dissolution the iron is incorporated into the normal body iron pool.

In a study of healthy volunteers, serial blood samples were taken from 15 subjects where 3 subjects each received Combidex at one of five doses: 0.3, 0.6, 0.8, 1.1 and 1.7 mg Fe/kg. Blood samples were collected prior to dosing and at 5, 10, 30 and 45 minutes and 1, 2, 4, 6, 12, 18 and 24 hours following administration. MR relaxation times showed that plasma levels were proportional to dose while half life and clearance were independent of dose.

In a clinical pharmacology study involving 18 healthy volunteers, serial blood samples were taken from 6 subjects (3 male, 3 female) each receiving Combidex at one of three doses: 1.1, 1.7 or 2.6 mg Fe/kg. Subjects were administered Combidex as an intravenous injection over a period of 13 to 16 minutes. Plasma drug concentration was determined from MR relaxation times at 5 minutes, 1, 4, 6, 12, 24 hours and 2, 3, 4, 5, 6, 7, and 14 days. MR imaging of the head and neck, lymph nodes, aorta, liver, spleen, bone marrow and muscle was also performed pre-dose and immediately post-dose, 24 and 72 hours and 7, 14 days and at 1, 2 and 3 months after administration or until the signal intensity of the organ of interest returned to its original baseline measurement. Based on AUC and C_{max}, plasma levels of Combidex were proportional to dose. Based on relaxivity measurements the mean AUC values of doses of 1.1, 1.7 and 2.6 mg Fe/kg were 46.4, 80.1 and 104.9 μg Fe/ml x days, respectively. C_{max} was 37.1, 52.6 and 70.1 μg Fe/ml. Half life and clearance were dose independent. The plasma half life of Combidex was approximately 25 to 30 hours. There were no differences between males and females with regard to any of the pharmacokinetic parameters analyzed. Signal intensity remained decreased for 1 day after the original administration of Combidex on T2 sequences for the liver and spleen and for 3 days after the original administration of Combidex on T2* sequences for lymph nodes.

Tissue distribution of Combidex was studied in rats following intravenous injection of ^{59}Fe radiolabeled Combidex at doses of 1.1, 2.2 and 3.4 mg Fe/kg. At 5 minutes post-injection in the radiolabeled study, the calculated blood volume contained at least 93% of the injected dose, which declined to 8 to 10% after 24 hours and then slowly rose over the remainder of the recovery period. After 1 day virtually all of the radiolabel in the blood was associated with the red cell fraction. The rise in blood radioactivity is due to normal utilization of the injected iron into hemoglobin after being metabolized into the normal body iron pool. Distribution of radiolabel to the tissues was greatest in the spleen, liver and lymph nodes and gradually decreased over time.

Metabolism: The iron in Combidex enters the normal body iron metabolism cycle as evidenced by transient increases in serum iron values one day after administration and in serum ferritin values 3 - 7 days after administration. The amount of iron contained in a single dose of Combidex (2.6 mg Fe/kg for a total dose of 182 mg Fe in a 70 kg individual) is less than the amount of iron contained in a single unit of whole blood. Serum iron increases at day 1 in a dose dependent manner, decreases towards baseline by day 3 and returns to normal range by day 7.

Special Populations:

Geriatric: Of the 947 subjects in US clinical studies of Combidex, 277 (29%) were 65 and over, while 56 (6%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric: Safety and effectiveness of Combidex has not been established in pediatric patients. Efficacy and dosing are expected to be the same as in adults based on the mechanism of action of the agent.

Gender: No differences in pharmacokinetics or pharmacodynamics were seen by gender. In the pharmacokinetic study, some gender differences were noted in iron metabolism measurements as expected from the different baseline iron status of men and pre-menopausal women. There are no apparent pharmacological actions at clinically relevant doses, exclusive of the utilization of the metabolized iron as an essential mineral.

Race: Pharmacokinetic differences due to race were not studied.

Renal Insufficiency: Combidex is not renally cleared; no studies were specifically designed to study patients with renal insufficiency. The incidence of adverse events for subjects with renal insufficiency (defined as a pre-dose creatinine level of 2.3 mg/dL or higher or a pre-dose BUN level of 42 mg/dL or higher) was similar to that for subjects without renal insufficiency, although the number of subjects in clinical studies with renal insufficiency was very small.

Hepatic Insufficiency: Patients with a history of cirrhosis had a higher incidence of adverse events including back pain, headache, nausea, urticaria, pruritus and chest pain.

Hemochromatosis: Individuals with iron overload were not studied. A single dose of Combidex contains less iron than a single unit of whole blood.

Drug-Drug Interactions: *In vivo* or *in vitro* drug interaction studies have not been conducted. The drug interaction potential resulting in changes in pharmacokinetics due to the use of Combidex is expected to be low because the iron enters the normal body iron metabolism cycle. However,

whether Combidex can inhibit or induce metabolic enzymes is not known. In rats, pretreatment with heparin did not prolong the half life of Combidex in the blood.

Dietary Effects: Clinical studies of Combidex including Pharmacokinetic studies (with the exception of the initial Phase 1 study) were performed with non-fasted subjects.

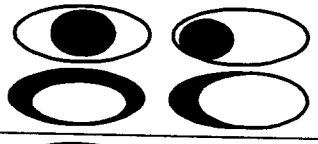
Pharmacodynamics:
Combidex is a superparamagnetic iron oxide that causes local magnetic field inhomogeneities resulting in increases in proton relaxation rates. These in turn cause signal loss (image darkening) on T2 weighted images and signal increases on strongly T1 weighted images. Combidex has a plasma half life of about 25 to 30 hours in humans and is eventually incorporated into the various organs of the reticuloendothelial system including liver, spleen, lymph nodes and bone marrow. In the late phase of distribution (24 to 36 hours after administration), the contrast agent allows imaging of lymph nodes by darkening normal lymph nodes on T2 weighted and T2* sequences.

An MRI with Combidex does not allow visualization of an increased number of nodes compared to unenhanced images.

Normal lymph nodes (nonmetastatic and inflammatory) contain macrophages which phagocytose Combidex. Twenty-four to thirty six hours after Combidex administration, normal lymph nodes appear dark on T2 weighted and T2* sequences due to the uptake of the iron oxide in the drug by macrophages. In metastatic disease, the macrophages in the lymph nodes are slowly replaced by tumor. In this situation, Combidex is not taken up by the macrophages and the nodes have high signal (appear white/bright with no blackening) on heavily T2 weighted or T2* MR images. As cancer is a progressive disease, the uptake of Combidex can vary producing various nodal patterns on MRI due to the decreased phagocytic activity within the lymph node as seen in the Combidex Lymph Node Imaging Guidelines.

Objective signal intensity measurements were taken of both metastatic and nonmetastatic nodes. For the metastatic nodes, signal intensities increased about 20% on T1 sequences and decreased about 20% on T2 sequences. For nonmetastatic nodes, signal intensity did not change on T1 sequences and decreased markedly by 48-58% on T2 sequences. The decreases seen on the T2 and T2* sequences were significantly larger for nonmetastatic nodes than for metastatic nodes with the greatest difference seen on the T2* sequences.

Combidex Lymph Node Imaging Guidelines

Post Dose	Description	Diagnosis
	No blackening of node or node is hyperintense to surrounding tissue; heterogenous or homogenous architecture	Metastatic
	Node has central high signal with darkening along the peripheral rim; heterogenous architecture	Metastatic
	Partial darkening whereby more than 50% of the node has area of high signal intensity; heterogenous architecture	Metastatic
	Less than 50% of node has high signal intensity; heterogenous architecture	Possibly Metastatic
	Node having an overall dark signal other than a central or hilar area of fat seen on T1 sequence; heterogenous architecture	Nonmetastatic
	Node having an overall dark signal with speckles of subtle granularities; homogenous architecture	Nonmetastatic
	Node having an overall dark signal intensity; homogenous architecture	Nonmetastatic

CLINICAL TRIALS

Lymph Node Studies

Combidex was evaluated in an open label multicenter study with 26 investigators in the United States at a dose of 2.6 mg Fe/kg body weight. In this study there were 152 patients (85 male, 67 female; 86% Caucasian, 11% black, 2% Asian, 1% other races; mean age 57 years; range 25-87) who had highly suspected or confirmed cancer with possible metastases to lymph nodes in the head and neck, breast, abdominal-pelvic and lung regions. Patients must have been scheduled for biopsy or surgery of at least one lymph node. Of the 152 patients, 134 had surgery or biopsy of lymph nodes. Histology showed 66 patients with metastases, 63 patients with no metastases and 5 patients in whom the nodal status was unknown. The drug product was diluted with saline and infused slowly infused at a rate of 4 ml/minute.

Each patient had magnetic resonance imaging of the area of suspected lymph node involvement within 14 days before the Combidex administration and 24 to 36 hours after administration of Combidex.

Two teams of Blinded Readers (each composed of a radiologist and an oncologist) with expertise in the body area imaged, read the pre-dose images alone, the paired pre- and post-dose images together and the post-dose images alone. The Blinded Readers evaluated lymph nodes visualized for the presence or absence of disease based on the uptake of Combidex by the lymph nodes.

When the blind read was completed, a radiologist who was not involved with the study matched the nodes identified by the Blinded Readers to nodes identified by the unblinded investigators that were evaluated histologically at surgery or biopsy to establish correlation of pathology and imaging on an individual nodal level. Each node was classified as metastatic or non metastatic using the Combidex Lymph Node Imaging Guidelines. (See **CLINICAL PHARMACOLOGY-PHARMACODYNAMICS section**). Sensitivity, specificity and accuracy were determined compared to unenhanced MR imaging using histologic findings.

Sensitivity, Specificity, Accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) on a Nodal Level: Blinded Evaluation

Blinded Reading	Evaluation	No. of Lymph Nodes	Sensitivity	PPV	Specificity	NPV	Accuracy
1	Pre-Dose (Size Dx)	173	54%	72%	82%	68%	69%
	Paired	173	83%	75%	76%	84%	79%
	Post-Dose	169	85%	83%	85%	87%	85%
2	Pre-Dose (Size Dx)	158	54%	76%	81%	62%	67%
	Paired	157	83%	80%	77%	80%	80%
	Post-Dose	147	84%	86%	84%	81%	84%
1 & 2 Average	Pre-Dose (Size Dx)	NA	54%	74%	82%	65%	68%
	Paired	NA	83%	78%	77%	82%	80%
	Post-Dose	NA	85%	85%	85%	84%	85%

Use of Combidex minimized the number of false diagnoses obtained with lymph node MRI. The post-dose images evaluated alone provided the best results on both a nodal and a patient level.

Total Number of False Positive and False Negative Diagnoses on a Nodal Level: Blinded Evaluation (BR)

	False Positive Nodes		False Negative Nodes		Total False Diagnoses	
	BR 1	BR 2	BR 1	BR 2	BR 1	BR 2
Pre (Size Dx)	17	14	36	38	53	52
Paired	22	17	14	14	36	31
Post	14	11	12	13	26	24

The number of false diagnoses is lowest with the use of Combidex enhanced images alone.

INDICATIONS AND USAGE

Lymph Nodes

Combidex is for intravenous administration as a contrast agent for use with Magnetic Resonance Imaging (MRI). Combidex can assist in the differentiation of metastatic and non metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases.

The information provided by Combidex should be considered in conjunction with other diagnostic information and lymph node findings from Combidex images should be pathologically confirmed unless medically contraindicated.

CONTRAINDICATIONS

Combidex is contraindicated in patients with known allergic or hypersensitivity reactions to parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations.

WARNINGS

A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating anaphylactic or anaphylactoid reactions should be available. Patients with a history of reactions to contrast media, other allergies, or immune system disorders should be observed for several hours after drug administration. Anaphylactic-like reactions and hypotension have been noted in some patients receiving iron and dextran formulations, or radiographic contrast media. Patients with autoimmune disease have not been studied with Combidex but have been reported in the published literature to have a high rate of adverse reactions to injectable iron-dextran formulations. If hypersensitivity, or moderate to severe pain occurs, the injection should be stopped and symptomatic treatment should be given.

PRECAUTIONS

GENERAL: THE DECISION TO USE CONTRAST ENHANCEMENT SHOULD INCLUDE A CONSIDERATION OF THE RISK OF THE DRUG, THE RISK OF THE PROCEDURE, THE EXPECTED BENEFIT OF THE IMAGE AND THE PATIENT'S UNDERLYING DISORDER. THE DECISION TO USE COMBIDEX SHOULD BE BASED UPON CAREFUL EVALUATION OF CLINICAL DATA AND OTHER RADIOLOGIC DATA.

Combidex must be administered by slow infusion over 15 to 30 minutes after dilution in 100 ml normal Saline. The incidence and severity of adverse events, including hypotension, is increased if the contrast agent is not administered diluted.

Combidex should not be used for nodal evaluation when the existing diagnostic work up, including anatomic imaging has adequately provided clinical nodal staging information. Combidex should not be used in patients with extensive lymphadenopathy or distant metastases.

Hypotension: Hypotension has been associated with the rapid administration of iron. These hypotensive reactions are not associated with signs of hypersensitivity and have usually resolve within one or two hors. Successful treatment may consist of observation, or if the hypotension causes symptoms, volume expansion. Do not administer Combidex by direct injection. **(See DOSAGE AND ADMINISTRATION section)**.

Patients receiving contrast agents, especially those who are medically unstable, must be closely supervised. Diagnostic procedures which involve the use of any contrast agent should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. After parenteral administration of a contrast agent, competent personnel, a fully equipped emergency cart or equivalent, and emergency facilities should be available for at least 60 to 120 minutes.

The possibility of a reaction including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered. Increased risk is associated with a known sensitivity to iron or dextran, history of previous reaction to a radiographic contrast agent, known allergies, other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or non-specific mediator release.
Skin testing cannot be relied upon to predict severe reactions and skin testing may itself be hazardous to the patient. A thorough medical history with emphasis on allergy and hypersensitivity, immune, autoimmune and immunodeficiency disorders, and prior receipt of and response to the injection of any contrast agent, may be more accurate than pretesting in predicting potential adverse reactions.

Combidex contains iron and should be used with caution in patients with disorders associated with iron overload (e.g., hemosiderosis, chronic hemolytic anemia with frequent blood transfusions). The incidence of pain related adverse events may be increased in frequency in patients with cirrhosis.

Caution during injection of a contrast agent is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease. Extravasation of the contrast agent was noted in two patients in clinical trials and both recovered with no residual effects.

Repeat Procedures: The safety of repeated doses has not been studied. If the physician determines that imaging needs to be repeated, based on the pharmacodynamics of Combidex, repeat images could be obtained up to 1 day after the original administration without re-injection for imaging well-perfused abdominal organs (T2 sequences only) and up to 3 days after administration for lymph node imaging (T2* sequences only). **(See CLINICAL PHARMACOLOGY section).**

Information for Patients

Patients receiving Combidex should be instructed to inform their physician or health care provider:

1. If they are pregnant or nursing.
2. If they are allergic to iron or dextran containing drugs or have had any reactions to previous injections of contrast agents. Also, patients should be instructed to inform their physician or health care provider if they have a history of allergies to any other drugs or food.
3. About all medications they are currently taking, including non-prescription (over-the-counter) drugs and vitamins.

Patients should be informed that:
1. Combidex has been prescribed for MRI enhancement.
2. The drug product is a dark color.
3. The skin surrounding the infusion site may discolor if there is extravasation; the discoloration should disappear over time.

Drug Interactions
Drug interactions were not noted and were not studied in clinical trials. Combidex administration provides elemental iron. In patients who are receiving supplemental iron orally, or parenterally, the dose of supplemental iron may need to be decreased. The effect of concomitant parenteral iron on Combidex dosing is not known. **(See CLINICAL PHARMACOLOGY section).**

Most drug metabolism by cytochrome P450 occurs in the endoplasmic reticulum of hepatocytes. In pre-clinical studies in rats and dogs, Combidex localizes in Kupffer cells. Its presence is detectable histologically only at high concentrations (400 mg Fe/kg). Specific drug interaction studies have not been conducted. However, based on a literature review of the effect of iron on cytochrome P450 at the recommended doses, Combidex would not be expected to have a major effect on the metabolism of concomitant drugs.

LABORATORY TEST FINDINGS

Combidex contains iron and iron metabolism determinations are consistent with normal metabolism of an iron injection. Serum iron and TIBC measurements may not be meaningful for 3 - 7 days following administration because of assay interference. Serum ferritin levels remain within normal

range, peak at 3 days after administration, and slowly return to baseline levels. Small transient decreases in transferrin were noted with no dose response effect.

Combidex produced no consistent, clinically significant effects on blood chemistry, hepatic function, electrolytes or ancillary tests. The changes that occurred were attributed to the patients' primary diseases, underlying conditions such as diabetes, concomitant medications or pre-existing laboratory abnormalities.

The effect of Combidex on immune function was evaluated in a placebo controlled clinical trial in 23 healthy subjects. Nineteen subjects received Combidex (9 male, 10 female) and four subjects received placebo. No effects on total white cells, lymphocytes, lymphocyte subtypes, natural killer cells and suppressor/cytotoxic T-cell activity were observed up to six months after administration of Combidex or placebo. There were no dose or time-dose related effects on any immunological parameter studied. Combidex had no immediate or delayed effect on immune function.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Long term animal studies have not been performed to evaluate the carcinogenic potential of Combidex. The results of the following genotoxicity assays were negative: the Salmonella/mammalian-microsome reverse mutation assay (Ames Test), the CHO/HGPRT forward mutation assay, the measurement of chromosomal aberrations in CHO cells, the assay for unscheduled DNA synthesis in rat liver primary cell cultures, the *in vivo/in vitro* rat hepatocyte DNA repair assay and the *in vivo* mouse micronucleus assay.

PREGNANCY

Pregnancy Category C.

Combidex administered intravenously to rats had no adverse maternal effects at 5 mg Fe/kg/day for 10 days but was maternotoxic at 15 and 50 mg Fe/kg/day as evidenced by increased liver and spleen weights and (at 50 mg Fe/kg/day) reduced body-weight gain, and mean daily food consumption. Combidex was not teratogenic at 5 and 15 mg Fe/kg/day. Teratogenic effects were observed at 50 mg Fe/kg/day, however, and were manifested by malformed limb bones and/or scalpulae.

There was no evidence of maternal toxicity when Combidex was administered to rabbits at a dose of 5 or 15 mg Fe/kg/day; slightly increased relative liver weights and one abortion were noted in the mid-dose group. Combidex was maternotoxic at 50 mg Fe/kg/day as evidenced by abortions in 13 out of 14 pregnant does between gestation days 15 and 25. No evidence of embryolethality was found at the 5 mg Fe/kg/day dose level. One rabbit at the mid-dose level and all 13 rabbits treated with Combidex at 50 mg Fe/kg that were necropsied due to signs of abortion revealed resorptions (three does in the high dose group had live fetuses, and two had dead fetuses). Combidex was not teratogenic in rabbits at a dose level of 5 mg Fe/kg/day, but did cause major malformations when administered daily at a dose level of 15 mg Fe/kg (bilateral bent femur and humerus). In all treatment groups, there were increased incidences of fetuses with fused sternebrae (a minor skeletal defect) and decreased spleen size. The total incidence of fetuses with external, soft-tissue, and skeletal defects was significantly increased at the 15 mg Fe/kg dose level. Insufficient litter data at the 50 mg Fe/kg dose level prevented a definitive teratologic evaluation at that dose level.

Adequate and well controlled studies were not conducted in pregnant women. Combidex should be used during pregnancy only if the potential benefit justifies the potential risk.

NURSING MOTHERS

It is not known whether Combidex is excreted in human milk. This drug should only be used in nursing women if the benefit clearly outweighs the risk.

PEDIATRIC USE

Safety, effectiveness, or pharmacokinetics of Combidex in pediatric patients below the age of 18 have not been established. Efficacy and dosing are expected to be the same as in adults based on the mechanism of action of the agent.

ADVERSE REACTIONS

In clinical trials a total of 2061 subjects (118 healthy volunteers and 1943 patients) received Combidex. Seventy five subjects received placebo in these studies. Combidex was administered by slow infusion following dilution in 100 ml saline in 1566 subjects, by dilution in 50 ml saline in 364 subjects and by direct bolus injection in 131 subjects. There was a higher incidence of adverse events such as hypotension, back, chest and abdominal pain and vasodilation with direct injection.

The most common adverse events that occurred with dilution in 100 ml saline and infusion were vasodilation (3.3%), rash (2.8%), back pain (2.5%), pruritus (2.4%) and urticaria (1.9%).

There was an increased incidence of pain related adverse events in patients with cirrhosis.

Hypersensitivity reactions including dyspnea, urticaria and laryngeal and facial edema were experienced in 79/2061 subjects who were administered. The majority (61%) of these reactions occurred within the 30 minutes of drug administration (that is, during infusion). In 10 of the patients with hypersensitivity reactions the event was managed by stopping the infusion. Most events were less than two hours in duration.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy are twice that of the general population. Patients with a history of previous reactions to contrast media are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

There was a higher incidence of adverse events such as vasodilation and back pain with less diluted doses, whereas the incidences of pruritus, rash and urticaria appeared unrelated to the method of administration.

Adverse events that occurred in greater than or equal to 0.5% of the 1236 subjects who received Combidex after dilution in 100 ml saline and infusion are listed below.

Adverse Events with dilute administration in ≥0.5% of the subjects at a dose of 2.6 mg Fe/kg.

Adverse Event	N = 1236
Vasodilation	3.4%
Rash	3.0%
Back pain	2.4%
Pruritus	2.2%
Urticaria	1.7%
Dyspnea	1.3%
Nausea	1.2%
Chest pain	1.1%
Pain	0.8%
Sweating	0.7%
Headache	0.6%
Overall	**15.8%**

The following adverse reactions were reported in <0.5% of the subjects receiving Combidex: BODY AS A WHOLE: asthenia, injection site edema/hematoma, injection site pain, neck pain, subcutaneous hematoma, hypothermia, malaise, scleroderma, eccymosis; CARDIOVASCULAR SYSTEM: arrythmia, bradycardia, hypertension, hypotension, palpitations, peripheral vascular disease, tachycardia, bradycardia; DIGESTIVE SYSTEM: dyspepsia, flatulence, cardiospasm, abnormal stool, tongue disorder; HEMIC AND LYMPHATIC SYSTEM: coagulation disorder, cyanosis; METABOLIC AND NUTRITIONAL SYSTEM: peripheral edema; MUSCULOSKELETAL SYSTEM: cramps, arthralgia, joint disorder, paresis, myalgia, hypotonia; NERVOUS SYSTEM: hypertonia, stupor, insomnia, nervousness, sleep disorder, somnolence, vertigo; RESPIRATORY SYSTEM: rhinitis, voice alteration, asthma, cough, larynx edema, hyperventilation, hypoxia, laryngismus, pharyngitis, respiratory disorder; SKIN AND APPENDAGES: maculopapular rash, erythema multiforme, skin discoloration; SPECIAL SENSES: conjunctivitis, eye disorder, abnormal vision, mydriasis, tinnitus; UROGENITAL SYSTEM: urinary incontinence, urinary tract infection, abnormal urine. **(See sections on CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).**

There were five patients (0.3%) who experienced serious adverse events with dilution in 100 ml saline and infusion that were related to the drug administration. There were 3/131 (2.3%) patients with serious adverse events who received the drug undiluted by direct injection. The rate of serious adverse reactions including hypotension is greater if the agent is administered rapidly by direct injection. One patient that received a direct bolus injection of Combidex died as an outcome to the adverse events. This was due to anaphylactic shock in a 70 year old patient with multiple body system disorders and a history of a previous allergic reaction to iodinated contrast media. The first in a series of adverse events occurred 1 to 2 minutes after receiving Combidex. Oxygen was administered immediately. Epinephrine and atropine were administered 9 minutes and 14 minutes, respectively, from the initial event during transfer to the emergency room from an outpatient imaging facility.

OVERDOSE

Overdose with Combidex has not been reported. Accidental administration of an entire vial of Combidex would result in a total dose of 210 mg of iron approximately equal to the amount of iron in a unit of whole blood. This contrast agent should not cause iron overload when used as directed.

DOSAGE AND ADMINISTRATION

Drug Preparation

1. Reconstitute with 10 ml of normal saline. Mix the reconstituted agent well (10-20 inversions) and draw up the appropriate dose of Combidex, based on body weight, into a sterile syringe.

2. Dilute the agent in 100 ml normal saline.

3. Administer the agent by slow infusion over 30 minutes using the filter provided.

The drug product should be administered immediately after reconstitution. If the product is to be used later reconstitution in a work area such as a laminar flow hood utilizing aseptic technique the drug product is recommended. Under these conditions the product may be stored up to 6 hours following reconstitution. Following reconstitution each vial contains 20 mg Fe/ml.

Dose: The recommended dose is 2.6 mg Fe/kg diluted with 100 ml of normal saline and administered at a rate of 4 ml/minute.

The contrast agent must be diluted in 100 ml normal saline and slowly infused.

Imaging: Post-contrast imaging may begin 24 hours after dosing and may be performed up to 36 hours after dosing. Pre-contrast imaging is not necessary.

HOW SUPPLIED

Each vial of Combidex contains 210 milligrams of iron, 631 milligrams of dextran and 27 milligrams of sodium citrate which has been lyophilized. The vial is to be reconstituted with 10 ml of normal saline. Following reconstitution the total volume is 10.5 ml containing 20 mg of iron/ml, 60 mg dextran/ml and 2.6 mg sodium citrate/ml. A single use administration filter is supplied for each vial. The container closure may be penetrated only one time, utilizing a suitable transfer device which will allow the withdrawal of two doses depending on the dosage and indication.

NDC#59338-7227-1 single vial
NDC#59338-7227-5 box of 5 vials

STORAGE

Store both reconstituted and unreconstituted drug vials at 25 °C (77 °F); excursions permitted to 15 - 30 °C (59-86 °F). The reconstituted product must be discarded after 6 hours. **(See DOSAGE AND ADMINISTRATION section)**.

Rx Only.

The following patents have claims directed to the drug: USP 4,770,183, USP 4,827,945, USP 4,951,675, USP 5,055,288, USP 5,160,726, USP 5,219,554, USP 5,262,176, USP 5,314,679.

Combidex® is a registered trademark of Advanced Magnetics, Inc.

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