

Appendix 7.4

Summary of Combidex Use and Imaging Procedure

PREPARATION, DOSAGE, AND ADMINISTRATION

1. Combidex is supplied as a lyophilized powder in a single use vial containing sodium citrate, dextran, and 210 mg of iron. The recommended dose is 2.6 mg Fe/kg patient weight.
2. **To reconstitute, the container closure may be penetrated only one time.**
3. **Combidity should be reconstituted using aseptic techniques then labeled with an expiration time and stored in an appropriately controlled environment. If the drug product will not be injected right after reconstitution, it is recommended to reconstitute it in a work area such as a laminar flow hood utilizing aseptic technique. Reconstitute the drug product with 10 ml of normal saline, (0.9% NaCl without a preservative). 10-20 inversions of the vial are recommended. Use a sterile syringe to draw up the appropriate dose based on body weight. Following reconstitution, each vial contains 20 mg Fe/ml. There is a total of 200 mg Fe in the vial.**
4. Dilute the agent in 100 ml of normal saline, (0.9% NaCl without a preservative). Only normal saline can be used as a diluent and flush. Combidity has a brown color. The i.v. bag containing the saline and the Combidity should be thoroughly mixed by manual manipulation and inversion techniques minimizing bubble formation.
5. **Combidity must be administered diluted through an open intravenous line at a rate of 4 ml/minute and must be infused through the filter provided.** An 18-22 gauge intracath is recommended for the infusion. The filter is attached inline between the Combidity/saline mixture and the i.v. access site in the patient.
6. Following administration of the contrast agent, an "open" intravenous line is maintained for at least 10 minutes to monitor and support the patient if hypersensitivity reaction occurs.
7. Shelf life of the reconstituted product is 6 hours. It must be stored at 59°-86° F and then discarded if not used within 6 hours of the reconstitution.
8. Patients receiving contrast agents should be closely monitored. After parenteral administration of a contrast agent, it is recommended that competent personnel, emergency equipment, and emergency facilities be available for 60-120 minutes. The patient should receive continuous single lead ECG and vital signs every 15 minutes during this time.
9. The safety of repeated doses has not been studied.

IMAGING PROCEDURE

TIMING: Imaging is performed 24-36 hours after administration of Combidex.

EQUIPMENT: Standard, FDA approved, MRI equipment used for imaging in the Phase 3 clinical trials.

US Phase 3 Study

GE, 1.5 T

GE Signa, 1.5T

Philips, 1.5T

Philips ACS II, 1.5T

Philips NT, 1.5T

Siemens, 1.5T

Siemens, 1.0T

Hitachi, 0.2T

EU Phase 3 Studies

GE 1.5T

GE MR Max, 0.5T

GE Horizon, 1.5T

Signa, 1.5T

Signa Horizon, 1.5T

Siemens Magnetom 1.5T

Siemens Vision 1.5T

Siemens Magnetom Vision 1.5T

Siemens Signa, 1.5T

Siemens Magnetom 1.0T

Siemens Magnetom Expert, 1.0T

IMAGING PARAMETERS:

Background

Combidex shortens T1 and T2*. Shortening T1 increases signal intensity and shortening T2* decreases signal intensity. As the indication for use of the contrast media is lymph node characterization in patients with known primary tumors that may metastasize to lymph nodes, examinations should be tailored to enhance T2* weighting. A long pulse repetition time (TR) and small flip angle (FA) are used to reduce T1 weighting. The echo time (TE) and number of sections set a minimum imaging time. It may be necessary to optimize acquisition parameters to enhance the accuracy of MR imaging for staging cancer in small nodes.

Imaging Protocols

1. Imaging must include the following sequences:
 - two-dimensional (2D) T1- Weighted Spin Echo
 - 2D T2 Weighted Spin Echo (Conventional or Fast)

- 2D Heavily Weighted T2* Gradient Echo.
2. Imaging parameters consist of routine MRI imaging protocols utilizing existing software that conforms to manufacturers' specifications for equipment and model. These include: number of excitations, pulse repetition times, echo times, flip angles, matrix, and field of view.
 3. **Accurate characterization of lymph nodes with Combidex requires high spatial resolution imaging.** Images should be collected using a Slice Thickness of ≤ 5 mm and Interslice Gap of ≤ 1 mm.
 4. Most subjects in the US and European clinical trials were imaged with thin sections in an axial plane.
 - For patients with **head and neck** cancer: axial images are obtained from the base of the skull to the supraclavicular region; coronal and sagittal images may also be obtained; a dedicated neck coil is recommended
 - For patients with **lung** cancer: axial images are obtained from the thoracic inlet to the top of the diaphragm; coronal and sagittal images may also be obtained; a body and/or surface coil is recommended
 - For patients with **breast** cancer: images of the area of interest may be acquired in any plane a body, breast or surface coil is recommended for imaging axillary or internal mammary nodes
 - For patients with **abdominal** cancer: axial images are obtained from the iliac crest through the pubic symphysis; a body coil, endorectal coil or pelvic phased array coil (or combination) is recommended
 - For patients with **prostate** cancer: axial images and oblique images in a plane parallel to the iliac vessels (obturator plane) are obtained
 - **Patients with a history of radiation therapy beyond six months are not excluded**
 5. Three dimensional (3D) T1-weighted gradient-echo sequence was mentioned in published reports by Harisinghani et al as additional sequencing for presurgical mapping of nodes. This author also referenced "adapted" three dimensional reconstruction techniques were being used in the clinical trials for display and analysis of the high resolution data.¹

¹ Harisinghani, MG et al, MR Lymphangiography: Imaging Strategies to Optimize the Imaging of Lymph Nodes with Ferumoxtran-10. Radiographics 2004; 3: 867-78.