

Tab 4 Introduction

4.1 Product Information

Combidex is an ultrasmall superparamagnetic iron oxide (USPIO) contrast agent covered with a low molecular weight dextran. Each vial contains 210 mg of iron, 631 mg of dextran and 27 mg of sodium citrate. The proposed use is 2.6 mg Fe/kg in 100 mL dilution with slow infusion (Please refer to Appendix 7.1 for the proposed product labeling).

Combidex has a long blood half-life in humans (approximately 25-30 hours). After initial vascular distribution, the product is incorporated into various organs of the reticuloendothelial system, including lymph nodes, and finally into the normal body iron pool. As a result, the product is currently being proposed for imaging lymph nodes in the late phase of distribution (24 to 36 hours after administration) to differentiate metastatic and non-metastatic nodes. The hypothesis is that normal or reactive lymph nodes, which possess macrophages that phagocytose the contrast agent, resulting in decreased signal intensity of those lymph nodes on post-dose MR images. Metastatic lymph nodes, in which normal tissue and macrophages are replaced by tumor, do not take up the contrast agent and hence do not show any change in signal intensity on post-dose magnetic resonance (MR) images.

Preclinical animal studies have shown a differential uptake between normal/hyperplastic nodes in comparison to malignancy. Preclinical studies have also suggested that signal decrease of lymph nodes in MR images can last as long as 28 days after a single administration of 1.1 or 2.2 mg Fe/Kg in animals. The effect this may have on the interpretation of imaging from repeat clinical dosing is unknown at this time.

4.2 Indication and Current Available Diagnostic Modalities

The sponsor has proposed the following indication for Combidex:

"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."

At this time, there are no FDA approved diagnostic drugs (contrast agents) that are specifically indicated for assisting the differentiation of metastatic vs. non-metastatic lymph nodes.

ProstaScint® (Kit for the preparation of Indium In 111 Capromab Pendetide), a radio-labeled monoclonal antibody, was approved by the FDA in 1997 as a diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer who are at high risk for pelvic lymph node metastases. In 152 patients who had an interpretable scan and pelvic lymph node pathology results, the product was associated with 62% sensitivity and 72% of specificity at the patient level.

Fludeoxyglucose (FDG) F 18 Injection is currently approved by FDA as a positron emission tomography (PET) agent for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities founded by other testing modalities, or in patients with existing diagnoses of cancer. Some preliminary data from the published articles has suggested that ¹⁸F-FDG were associated with approximately 90% sensitivity and specificity for lymph node assessment. Most of those studies, however, were only limited to non-small cell lung cancer. Given the fact that ¹⁸F-FDG PET relies on rates of glycolysis, it is likely that the performance of this agent may vary among different types of tumors.

One agent in the same drug class (USPIO), called ferumoxides injectable solution, is currently approved and marketed in the US under the trade name of Feridex I.V, as an adjunct to MRI in detection and evaluation of lesions of the liver. The product insert specifically states, however, that the product is not sufficient in distinguishing between types of lesions or diseases. We are not aware of any reported off-label uses of this product for differentiating metastatic and non-metastatic lymph nodes.

Non-contrast imaging modalities that are currently used for the evaluation of lymph nodes include Ultrasound, CT and MRI. The use of Ultrasound is limited to the head and neck area. The assessment of lymph nodes using CT and MR relies on nodal anatomy rather than function or physiology. The primary indication of metastases is lymph node size. While typically nodes > 10 mm are considered metastatic, the sensitivity and specificity of a size-based evaluation relies on the threshold of each radiologist. A low size threshold provides higher sensitivity with lower specificity and a higher size threshold lowers the sensitivity but improves specificity. Please refer to a

recently published article by Dr. Torabi, for a discussion on "Current Concepts in Lymph Node Imaging" (Appendix 7.2)

In addition to size, the radiologist who interprets the imaging results in clinical practice may also use other imaging features, such as location of the node with respect to the primary tumor, shape of the node, architecture, and nodal groupings, to determine if a node is metastatic. In clinical practice the consequences of a false positive or a false negative reading influence the way that MR scans are read by radiologists. Radiologists recognize that MR imaging is not a substitute for biopsy and may deliberately over-read the scans. They are willing to accept a low specificity (high false positive rate) in exchange for a very high sensitivity. If a node is considered suspicious and its status is critical to patient management it will be biopsied. The worst consequence of a false positive is an unnecessary biopsy, whereas the consequences of a false negative may be mis-diagnosis, mis-treatment, and failure to cure the patient's cancer.

Comments: *In general, knowing whether or not a lymph node is metastatic is very important. The presence of nodal metastases may limit the therapeutic options and also generally is associated with a worse prognosis. Approving a drug product (i.e., a contrast agent) for such a purpose, however, requires the following considerations:*

First, knowing nodal status may not necessarily change the American Joint Committee on Cancer (AJCC) stage groupings and/or therapeutic decisions for some cancer patients. This is particularly true for the patients who have already had a distant metastasis. For example, any breast cancer patients with a T4 lesion will be classified as Stage IIIB under AJCC regardless of nodal status. Any patients with a distant metastasis will be at Stage IV regardless of nodal status or size of the primary tumor. This consideration is important because all drugs (including diagnostic contrast agents) are associated with certain levels of risk. Depending on the type and severity of the risks, the use of a drug product (including a contrast agent) under certain clinical scenarios may have an unfavorable benefit/risk ratio.

Secondly, because of availability of relatively low-risk non-contrast imaging modalities, such as Ultrasound, CT and MRI, for the evaluation of lymph nodes, it is important for a contrast agent to offer an "added" clinical benefit or value.

Last but not least, a contrast-enhanced MR, like any other imaging modality, will always be associated with certain levels of uncertainty (i.e., the false negative and false positive cases) in differentiating metastatic and non-metastatic nodes. It is extremely important to ensure that such a limitation

is well understood and the test is not designed to replace a pathology-confirmation, if such a confirmation is important in determining patient's management or therapeutic options.

4.3 Overview of Clinical Development Program

Combindex is being developed in the US by Advanced Magnetics. An identical product with the trade name Sinerem is being developed in Europe by Guerbet. Both studies performed in the US by Advanced Magnetics and studies sponsored in Europe by Guerbet have been submitted in support of this application.

The original NDA submission (12 December 1999) contained 13 Phase 1-3 studies sponsored by Advanced Magnetics for three potential clinical indications, lymph node imaging, liver/spleen imaging, and MR Angiography. In addition, four Phase 2-3 European studies sponsored by Guerbet were also included. Table 4.3.1 lists those studies in the original NDA submission.

Table 4.3.1 Overview of Combindex Clinical Development Program

Indication	Phase	Site	# Dosed	Protocol #
Safety and PK Studies	1	US	69	180549-1, 38804-13, and 38804-17
Lymph Node	2	US	96	38804-(2,3,4), 38804-5, 38804-7, 38804-9
		EU	30	ALS-3-3-A
	3	US	152	38804-10
		EU	181	ALS-3-2-A, ALS-3-7-A, and ALS-3-10-A
Liver/Spleen	2	US	104	38804-06
	3	US	193	38804-8A and 38804-8B
MR Angiography	2	US	13	38804-12 and 38804-14

Source data: Modified based on information from page 35, Original NDA submission, Volume 1.56
dosed: number of patients received Combindex or Sinerem

This NDA resubmission (29 September 2004) lists a total of 16 new studies, including final study reports from three European studies. Since the remaining 13 studies were still on-going at time of this resubmission, only a safety evaluation is conducted based on the adverse events data collected prior to May 31, 2004.

The design and results of the Phase 3 studies will be discussed in detail

under Section 5 of this briefing document. Here are the brief summaries of Phase 1 and 2 studies:

- A selection of a dose of 2.6 mg Fe/kg and an imaging time of 24 to 36 hours were determined by a phase 2 study (Protocol 38804-7);
- A group of Phase 2 studies also suggested that the signal intensity of benign lymph nodes was substantially lower than that of metastatic nodes on post-dose images in patients with cancer of the head and neck, lung, breast, and pelvis (Protocols 33804-2, -3, -4, and -9)

4.4 Review of Regulatory History

The following is a list of major events related to clinical development of Combidex:

- February 1992 – the sponsor filed an initial IND with the FDA
- August 1996 – the sponsor submitted the study protocol for the US Phase 3 study
- September 1998 – the sponsor submitted the finalized statistical plan, including blinded read manual, for the US Phase 3 study to the FDA
- December 1999 – the sponsor filed the original NDA
- June 2000 – FDA issued an “approvable” letter, citing the deficiencies identified from both safety and efficacy evaluations
- September 2004 – the sponsor filed a complete response to the approvable letter

Comments: *In the original NDA submission, the sponsor was seeking the following two indications:*

- *Combidex is for intravenous administration as a contrast agent for use with Magnetic Resonance Imaging (MRI). Combidex is intended for use in patients that have highly suspected or confirmed primary cancer to assist in the differentiation of metastatic and nonmetastatic lymph nodes and to assist in clinical nodal staging. The information obtained from evaluation with Combidex may be useful in directing biopsy or surgery*
- *Combidex is for intravenous administration as a contrast agent for Magnetic Resonance Imaging (MRI) for the detection characterization and diagnosis of focal lesions in well perfused abdominal organs (liver and spleen)*

In FDA’s “Approvable Letter”, the following deficiencies were identified for the lymph node indication:

Efficacy Deficiencies: At least one additional robust study in an appropriately defined clinical setting must be completed and provide adequate evidence of clinical relevance because of:

- Lack of improvement in sensitivity seen with Combidex over non-contrast MR images when radiologists used their skill in interpreting node status (metastatic vs. non-metastatic);
- Inconsistent efficacy results in US and European trials; and
- Lack of identification of conditions of use

Safety Deficiencies: Lack of sufficient evidence of safety to justify the safe use under the proposed labeling conditions. Combidex is associated with fatal anaphylaxis, generalized allergic syndromes, and pain syndromes that required discontinuation of the infusion.

In general, the sponsor has not demonstrated that for what patient population with what conditions, and for what purposes, Combidex administration would produce a clinical benefit that outweighs risks.

The deficiencies with liver imaging indication are not listed here because the sponsor has decided not seek this indication with this resubmission.