

## **Tab 2      Executive Summary**

Combidex is a dextran-coated iron-based magnetic resonance (MR) contrast agent that is being proposed for assisting the differentiation of metastatic and non metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases. The proposed use is 2.6 mg Fe/kg given intravenously in 100 mL saline dilution over 30 minutes.

To support the proposed indication, the sponsor (Advanced Magetics, Inc) has submitted the efficacy results of two predefined primary analyses from data collected in one US and three European Phase 3 trials. While 152 and 181 patients with suspected or confirmed primary cancer of the head & neck, lung, breast, abdomen and pelvis received Combidex in the US and European trials, the primary analyses were only based on approximately 128 pathology-confirmed cancer positive and 103 cancer negative lymph nodes. FDA is currently seeking the information on how many of those patients were actually included in the primary analysis. In those studies, MR images were taken prior to (pre-dose or non-contrast images) and after Combidex administration (post-dose or Combidex-enhanced images). Those images were evaluated blindly by two independent radiologists and the sensitivity and specificity of radiological interpretation of pre-dose MR images and post-dose MR images were calculated and compared, by using the pathology results as the truth standard.

In both US and European studies, when radiological interpretation was based on Combidex Imaging Guidelines (a pictogram developed by the sponsor to aid the interpretation of the Combidex-enhanced images), Combidex showed 83-85% sensitivity and 76-92% specificity (point estimates) for differentiating metastatic and non-metastatic lymph nodes. The level of performance was preserved even for those lymph nodes that appeared less than 10 mm on non-contrast MR images, which is a typical cut-off for non-metastatic by radiologists. The level of sensitivity could make Combidex attractive to identify additional metastatic lymph nodes among those less than 10 mm on non-contrast MR images that would otherwise be classified as non metastatic by the radiologists by using the 10mm cut-off. It is important, however, to emphasize that Combidex-enhanced MR imaging cannot be used to replace biopsy for confirming the nodal status because the imaging procedure is still associated with approximately 20% false negative rate (1-specificity, i.e., 1-80%) for those nodes.

In clinical practice, the radiologists could use more information (in addition to size) on non-contrast MR images to make radiological interpretation and they may deliberately over-read the scans, willing to accept a low specificity in exchange for a very high sensitivity (low false negative rate). This is

because consequences of a false negative may be serious, such as mis-diagnosis, mis-treatment and failure to cure the patient's cancer. In both US and European studies, radiological interpretation made by two blinded reader, using Combidex Imaging Guidelines, were associated with 13%-54% (point estimates) improvement in specificities, compared to that made by using all information available on non-contrast images. Data suggested that Combidex-enhanced MR imaging could still be useful under those clinical scenarios because it's improved specificity over non-contrast MR images. When the radiologists over-read non-contrast MR images, there will be many false positive lymph nodes identified. Because of the improved specificity, Combidex could be used to identifying the most appropriate lymph node for biopsy.

Here are, however, some efficacy issues that may affect validity of the efficacy findings in US and European studies.

- FDA has noted that the Combidex Imaging Guidelines – the key instrument used for interpreting contrast-enhanced images, were developed by using the same database that was later used to confirm the efficacy of Combidex-enhanced images (the US Phase 3 study). The primary concern is lack of the independence between test instrument (the Combidex Imaging Guidelines) from the materials (the US Phase 3 data) that was being tested. At this time, we do not know how many nodes from the Phase 3 US trial were being used in the development of the Combidex Imaging Guidelines. The sponsor has stated that the number was small and will present that information during upcoming meeting on March 3<sup>rd</sup> 2005. FDA may not have had an opportunity to evaluate that data.
- In the European studies, a different guideline was used by the radiologists during the blinded evaluation of the images. The interpretation of Combidex-enhanced images was made later by the sponsor who retrospectively correlated the information from the two Guidelines. Similarity of those two Guidelines needs to be further discussed by the MR experts of the Advisory Committee.
- Another factor that may affect the validity of the studies is that a relatively small fraction of lymph nodes visualized on MR images was included in the primary analyses because of difficulty in obtaining and correlating pathological diagnosis of the nodes and because of the inter-reader variability. It is uncertain whether the results from the primary analyses are applicable to all the tumor types that participants had in clinical trials. Moreover, there is no information on the type of non-metastatic nodes that were included in the primary analyses. It is also

uncertain whether inflammatory, infectious, or granulomatous processes were adequately represented.

If the results are found to be valid for the cancer population that were studied in the clinical trials, the question still remains whether the results are also applicable to other tumors that were not studied since the sponsor has requested a general indication without any restrictions to cancer types.

The key safety issue with the administration of Combidex is the risk of anaphylactic/anaphylactoid reactions. Of 131 patients who received direct bolus injection of Combidex, one patient died of such a reaction immediately post dosing, and 2 other patients experienced non-fatal reactions that were reported to be serious by the principal investigators. Of 1,236 patients who received Combidex diluted in 100 mL saline with slow infusion over 30 minutes, there have been no deaths but five subjects experienced a serious reaction. There is preliminary evidence suggesting the dilution with slow injection might reduce the incidence of serious anaphylactic/anaphylactoid reaction from 2.3% (3/131) to 0.4% (5/1,236). This reduction is less impressive when an anaphylactic/anaphylactoid reaction is operationally defined as any immediate hypersensitivity reaction that involved two or more body systems regardless of level of seriousness. By that definition, the incidence rates of anaphylactic/anaphylactoid reaction are 2.3% (3/131) and 1.1% (13/1,236), respectively, for patients with direct bolus injection and patients with 100 mL dilution with slow infusion.

Hypersensitivity reactions occur with all iron dextran products that are indicated for therapeutic purposes. It was reported that the incidence rate of the life-threatening reactions occurred in approximately 0.6% patients. Majority of those reactions occurs after the initial dose. There have been 18 post-marketing reports of death that were directly associated with anaphylactic/anaphylactoid reaction from the use of iron dextran products.

At this time, risk management strategies are limited. A test dose is proposed in the product labeling of the approved iron dextran products. The effectiveness of such a strategy has never been demonstrated. In the post-marketing reports, there were deaths that occurred with the test doses. While female or younger (age < 65) subgroups were associated with a higher incidence rates of the reactions from Combidex clinical database, it might not be practical to restrict the use based on those criteria.

It is still unclear whether the anaphylactic/anaphylactoid reactions are due to direct mediator releasing effects of iron (or dextran) or based on an IgE-mediated mechanism. There are no human laboratory data from Combidex clinical development program to answer this question. While the medical

treatment for those two types of reactions remains the same, we are interested in any preventive methods, such pre-treatment with certain drug products, that might mitigate the risk.

The data to support efficacy of Combidex should be evaluated in light of our current understanding of its risks. Like any other drug products, Combidex should only be used in a defined patient population where the demonstrated benefit clearly outweighs the risks.