NDA 21-115 (Combidex)
Oncology Drug Advisory Committee Meeting
March 3, 2005

Advanced Magnetics is proposing - *"Combidex is for intravenous administration as a contrast agent for use with 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 NDA includes data sets from US and European studies with readers performing radiological interpretation blinded to pathology results. Of 152 and 181 patients who received Combidex in the US and European studies, only 65% and 27% of patients were included in the primary analysis, respectively. The major tumor types included in the primary analysis of the US study were head & neck (n=27), breast (n=20), and lung (n=25). The primary analysis of the European studies included mainly head & neck cancer patients (n=37). In addition, the primary analyses also included 5 prostate cancer patients each from the US and European studies and a small number of other types of cancers.

The primary analysis was conducted at a nodal level. In the US trial, Combidex was associated with statistically significant improvement in sensitivity, compared to that of size-based interpretation of non-contrast MR imaging. The improvement was not observed in the European studies because the majority of nodes in those studies were larger than 10 mm. Further analyses showed that the performance of Combidex varied among tumor types and nodal sizes. The point estimates for sensitivity varied from 76% to 100% with the lower bound of 95% CI being as low as 55%. The point estimates for specificity varied from 44% to 91% with the lower bound of 95% CI being as low as 21%. In the US study, the point estimates for sensitivity and specificity were 68% and 80% for the nodes < 10 mm, and 95% and 64% for nodes > 10 mm.

Advanced Magnetics also submitted a study of Combidex in prostate cancer patients published in the New England Journal of Medicine to provide additional efficacy data. The study was a pooled analysis of two subgroups of prostate cancer patients from two on-going studies in the US and Europe. At this time, it is unclear how the patients in this analysis were selected. More importantly, the required source documents, including predefined statistical plan, blinded reader manual, and the original copy of the blinded reader's efficacy evaluation, are not available to the Agency. Therefore the Agency is unable to conclude that this study was conducted in accordance with Federal Regulations pertaining to new drug applications.

Of 2061 patients who received Combidex in the clinical development program, 1236 (60%) received the proposed clinical dose (2.6 mg Fe/kg) under the proposed method of administration (dilution in 100 cc and slow infusion over 30 minutes). In that group, immediate hypersensitivity reactions occurred at a rate of 5.3% (66/1236), with 2 patients having serious adverse events, and 19 patients needing treatment with steroids. There was one death due to anaphylaxis when Combidex was administered via direct injection. While no deaths have been observed in the patients with the proposed method of administration, the level of assurance is limited by the size of the current safety dataset.

Discussions and Questions

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For Discussion:

1. Please discuss the evidence for efficacy and any concerns about the validity and generalizibility of the study findings to support the use of Combidex for detection of lymph node metastases from all tumor types in all clinical settings, including *de novo* tumors and tumor recurrences.

2. Please discuss the differences in the potential clinical benefit of Combidex for nodes identified by prior imaging that are less than 10 mm, compared to nodes that are greater than 10 mm.

Questions:

1. Do the data demonstrate efficacy of Combidex for differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases?

2. Are the data robust enough to support use for a specific tumor type(s)? If yes, please identify the tumor type(s)?

3. Do the data demonstrate that Combidex is safe?

4. Do the data demonstrate that Combidex is safe and effective for marketing approval based on the sponsor's proposed indication?

   If yes, are there postmarketing studies you would recommend?

   If not, do the data demonstrate that Combidex is safe and effective for marketing approval for any other indication?

      If yes, please describe the patient population and clinical setting for which Combidex would be indicated?

      If no indication is supported by the current data, please recommend what additional studies or data are needed?