FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

March 13, 2006
Oncologic Drugs Advisory Committee (ODAC) Meeting
Gaithersburg Hilton, Gaithersburg, MD

FDA Questions for the ODAC
PM session: Gemzar® in Ovarian Cancer

sNDA: 20509/039

DRUG: Gemzar® (gemcitabine HCl)

APPLICANT: Eli Lilly and Company

PROPOSED INDICATION: "Gemzar in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy."

EXECUTIVE SUMMARY

Gemzar was studied in a randomized Phase 3 study of 356 patients with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized 1:1 to receive either Gemzar in combination with carboplatin (GC) or carboplatin (C) alone. The Gemzar/carboplatin combination improved progression-free survival (HR 0.72, p=0.0038, median 8.6 months for GC and 5.8 months for C) with no apparent effect on survival (HR 0.98, p=0.898) at a cost of increased toxicity, mainly anemia, neutropenia and thrombocytopenia, requiring increased RBC and platelet transfusions and increased use of granulocyte stimulating factors and erythropoietic agents. Independently assessed tumor response rates were Gemzar/carboplatin 46.3% and carboplatin alone 35.6%.

The main issue is whether this improvement in progression-free survival (PFS) without a demonstrated survival advantage and with the toxicity described above is sufficient basis for approval of this supplemental NDA. An important consideration is that the combination of paclitaxel and carboplatin has been shown in a randomized controlled trial (RCT) to prolong survival in this setting. In addition there is strong suggestive evidence from a RCT that liposomal doxorubicin prolongs survival in this population.

1. Does the committee agree that there are chemotherapy regimens that have been shown in randomized controlled trials (RCTs) to prolong survival in the patient population for the proposed indication, i.e. patients with advanced ovarian cancer that has relapsed 6 months or more after completion of platinum-based chemotherapy?

2. If given after progression, subsequent chemotherapy or cross-over may confound survival analyses and may obscure the demonstration of a survival improvement. Are there chemotherapy regimens that have been shown in RCTs to prolong survival if given after progression in the same patient population as in the Gemzar RCT?

3. In the Gemzar RCT, PFS was improved in the combination group without an apparent survival improvement (HR 0.72, median 8.6 months for GC and 5.8 months for C, LR p=0.0039). However, there was no apparent effect on survival (HR=0.98, p=0.898, medians 17.97 months for GC and 17.31 months for C). Eighty percent of the survival events have occurred.

   Is the demonstrated increase in PFS without an effect on survival and with the observed toxicity a sufficient basis for regular approval of Gemzar in combination with carboplatin for treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy?