Questions for the Gastrointestinal Drugs Advisory Committee
June 26, 2000

Novartis Pharmaceuticals Corporation has requested approval for Zelmac™ (tegaserod) Tablets for the treatment of irritable bowel syndrome (IBS) in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms. The sponsor recommends a dose of 6 mg po BID within 30 minutes prior to a meal.

1. Has efficacy been demonstrated in both men and women with constipation-predominant IBS?

   (a) If not, in which gender was efficacy demonstrated?

   (b) If yes (for both genders or one), which of the following dose(s) demonstrated efficacy?

      (i) 4 mg/day
      (ii) 12 mg/day
      (iii) titrated dose regimen from 4 mg/day to 12 mg/day

2. Please comment on the following findings of the carcinogenicity studies.

   (a) Mucosal hyperplasia and adenocarcinoma of the small intestine were observed in (CD-1) mice at the tegaserod dose of 600 mg/kg/day but not at 200 or 60 mg/kg/day.

   (b) An apparent increased incidence of ovarian follicular cysts at 110 weeks of age was observed in (HanIbm Wistar) rats.

3. In the clinical trials, diarrhea was seen in greater proportion in patients receiving Zelmac™. Please comment on this finding.

4. In the clinical trials, lower abdominal pain leading to laparotomy occurred in greater proportion in patients receiving Zelmac™. Please comment on this finding.

5. On the basis of your benefit-risk evaluation, do you recommend that Zelmac™ be approved for the indication requested by the sponsor?

   (a) If yes,

      (i) what labeling recommendations do you have to reduce the potential risks of Zelmac™?
      (ii) what recommendations do you have for post-marketing studies or risk management programs to address any remaining concerns?

   (b) If not, what additional efficacy and/or safety data should the sponsor provide?