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March 30, 2006

OVERNIGHT COURIER 3/30/06

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Gemcitabine for Injection USP, 2 gm/vial, is suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Gemcitabine for Injection USP, 2 gm/vial, is suitable for submission in an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Gemzar® (gemcitabine) for Injection, 1 gm/vial by Eli Lilly and Company. In addition, the petitioner also refers to the approved 200 mg/vial strength of gemcitabine listed in the Orange Book in support of this petition. Therefore, the petitioner seeks a change in strength (i.e., total drug content, from 1 gm to 2 gm), from that of the reference-listed drug product. From an historical perspective, the Agency has always treated petitions for injectable products that propose a different total drug content as the RLD as a change in strength, even if the final concentration of the proposed product is the same as that of the RLD.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in dosage strength from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, Gemzar® for Injection, by Eli Lilly and Company, is a lyophilized powder containing 1 gm of gemcitabine hydrochloride (expressed as free base) in a 50 mL sterile, single-use vial.[1] See listing **from the current version of the electronic Orange Book *Approved Drug Products with Therapeutic Equivalence Evaluations***, accessed on March 30, 2006, which also lists the approval of the 200 mg strength containing 200 mg of gemcitabine in a 10 mL sterile, single-use vial (Attachment 1).[2] The proposed drug product also represents a lyophilized powder form, but containing total drug content of 2 gm of gemcitabine in a 100 mL sterile,

single-use vial. The inactive ingredients in the proposed product will be qualitatively the same and quantitatively proportional to the inactive ingredients contained in the RLD. See comparative formulation summary (Attachment 2). The petition is thus seeking a change in strength (i.e., total drug content, from 1 gm to 2 gm), from that of the reference-listed drug. Please note that the proposed change in strength will yield a gemcitabine concentration of 38 mg/mL upon reconstitution with 0.9% Sodium Chloride Injection (w/o preservative), the diluent recommended in the approved labeling for Gemzar®. This is identical to the drug concentration that results from reconstitution of the approved 200 mg and 1 mg dosage strengths, as the approved labeling instructs that the strengths be diluted proportionally.

The approved labeling for the RLD list three indications for gemcitabine as follows:

> *Breast Cancer -- Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.*
>
> *Non-Small Cell Lung Cancer -- Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.*
>
> *Pancreatic Cancer -- Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.*

The acceptability of the proposed 2 gm strength is contemplated in the labeling of the 1 gm RLD and the approved 200 mg product. (Please note that both of the approved strengths are covered in a single package insert.) The indication-specific dosing instructions in the approved labeling for gemcitabine hydrochloride are as follows:

> *"Pancreatic Cancer -- Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks."*
>
> *"Non-Small Cell Lung Cancer -- Two schedules have been investigated and the optimum schedule has not been determined (see CLINICAL STUDIES). With the 4-week schedule, Gemzar should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemzar on Day 1."*
>
> *"Breast Cancer -- Gemzar should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts."*

The average Body Surface Area (BSA) of an adult male is 1.9 m^2 while the average BSA for an adult female is 1.7 m^2.[5] Using these figures, the total dose of Gemcitabine to be administered in a cycle day during the initial cycle of therapy is as follows:

Indication	Dose for average adult male	Dose for average adult female
Pancreatic Cancer	1.9 gm	1.7 gm
Non-Small Cell Lung Cancer *4-week schedule* *3-week schedule*	 1.9 gm 2.4 gm	 1.7 gm 2.1 gm
Breast Cancer	2.4 gm	2.1 gm

For all approved indications, the patient is monitored for hematologic toxicity via a complete blood count (CBC) and differential platelet count prior to commencement of each dose. In non-small cell lung cancer patients and breast cancer patients, the dose can be adjusted to 50% or 75% of the recommended full dose based on agranulocyte count (AGC) and platelet count results. For pancreatic cancer patients, the dose can be adjusted to 75% of the recommended full dose based on AGC and platelet count results. For pancreatic cancer patients who complete a full cycle of therapy, the dose for subsequent cycles can be increased by 25% based on evaluation of AGC, platelet nadirs and non-hematologic toxicity, and an additional 20% for cycles thereafter using the same criteria. The following table summarizes the recommended dosage adjustments after successful completion of the initial cycle of therapy:

Indication	Dose for average adult male	Dose for average adult female
Pancreatic Cancer, 1st set of subsequent cycles	2.4 gm	2.1 gm
Pancreatic Cancer, secondary set of subsequent cycles	2.9	2.5 gm

The above demonstrates that doses of 2 gm or greater are covered under the conditions of use prescribed in the approved labeling. Moreover, the availability of a 2 gm vial will be more convenient for a healthcare professional administering the infusion and will reduce the amount of waste that is presently being generated by the use of multiple vials for delivery of prescribed doses.

The proposed changes in the labeling are limited to the addition of strength sought in this petition. Additionally, the directions for reconstitution have been expanded to include proportional dilution of the contents of the 2 gm vial with the recommended diluent. The uses, indications, warnings and directions for use will remain the same as that of the RLD. Draft labeling for the proposed product is included as Attachment 3. The approved labeling for the RLD (which is common to the 200 mg, 1 gm, and 2 gm strengths) is included as Attachment 4.

Applicability of Pediatric Research Equity Act

The Pediatric Research Equity Act (PREA), which was singed into law on December 2, 2003, requires that all applications for approval of a new active ingredient, indication, dosage form, dosing regimen or route of administration contain a pediatric assessment unless the applicant has obtained a waiver or deferral under Section 505(B)(b). If the pediatric assessment requires the conduct of clinical studies, the application will be ineligible for submission as an ANDA. This petition is being submitted in support of a new **dosage strength** for use in accordance with the conditions prescribed in the approved labeling for the RLD. It does not encompass a new dosing regimen or any of the other eligibility criteria for the conduct of pediatric studies. Accordingly, the product that is the subject of this petition is exempt from the requirement for a pediatric assessment.

In consideration of the above, the petitioner's request for the Commissioner to find that a change in strength from 1 gm/vial to 2 gm/vial, for Gemcitabine for Injection, USP should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Joan Janulis
Director

JJ/pk

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Version, accessed March 30, 2006
2. Comparative Formulation Data
3. Draft Insert Labeling Proposed for Gemcitabine for Injection USP, 2 gm/vial
4. Labeling for Gemzar® for Injection

cc: Leo Zadecky (OGD)

F02JD6089

[1] Gemzar® for Injection, 1 gm/vial also contains mannitol (1 gm), sodium acetate (62.5 mg) and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

[2] Gemzar® for Injection, 200 mg/vial also contains mannitol (200 mg), sodium acetate (12.5 mg) and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

[3] The 200 mg strength is reconstituted by adding 5 mL of 0.9% Sodium Chloride Injection to the vial to yield a total volume of 5.26 mL. (The powder upon reconstitution displaces 0.26 mL.) The 1 gm strength is reconstituted by adding 25 mL of 0.9% Sodium Chloride Solution to the vial to yield a total volume of 26.3 mL. (The powder upon reconstitution displaces 1.3 mL.) The proposed 2 gm strength will be reconstituted by adding 50 mL of 0.9% Sodium Chloride solution to the vial to yield a total volume of 52.6 mL. (The powder upon reconstitution displaces 2.6 mL.)

[4] Reference: Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.