



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

---

Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Pediatric and Maternal Health Staff Review – Pediatric Team Review**

**Date:** November 16, 2010                    **Date Consulted:** October 8, 2010

**From:** Jeanine Best, MSN, RN, PNP  
Senior Clinical Analyst, Pediatric and Maternal Health Staff

**Through:** Hari Cheryl Sachs, MD  
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.  
OND Associate Director, Pediatric and Maternal Health Staff

**To:** Division of Drug Oncology Products (DDOP)

**Drug:** Gemcitabine Injection, NDA 200-795

**Subject:** Pediatric Use Labeling

**Materials Reviewed:**

- Draft Gemcitabine Injection labeling, NDA 200-795
- Orange Book Patent and Exclusivity Information for Gemzar, NDA 20-509

**Consult Question:**

The purpose of this consult request is to ask for PMHS to assist with review of the pediatric language regarding negative studies in the proposed gemcitabine 505(b)(2) labeling for NDA 200795. DDOP proposes removal of information protected by pediatric exclusivity in the Gemzar label, which is not expected to affect safe use of the drug. DDOP recommends that for 505b2 drugs for Gemzar, only the sentence “The safety and effectiveness of Gemzar in pediatric patients has not been established” remain in the label at this time.

## **INTRODUCTION**

Hospira, Inc. submitted a 505(b)(2) NDA (200-795) for Gemcitabine Injection on December 11, 2009. The Reference Listed Drug (RLD) is Gemzar (gemcitabine hydrochloride) Injection, Powder, Lyophilized, For Solution For Intravenous Use, (NDA 20-509, Eli Lilly & Company). The Division of Oncology Drug Products (DDOP) extended the review clock and the current PDUFA date is January 11, 2011. The proposed changes in the labeling for this 505(b)(2) product are limited to a change in the dosage form (a ready to use aqueous solution), removal of mannitol and sodium acetate as inactive ingredients, and the addition of a 2 g strength.

This new gemcitabine dosage form (a ready to use aqueous solution) triggered the Pediatric Research Equity Act (PREA). Hospira, Inc. submitted a full waiver for pediatric studies at the time of NDA submission and was subsequently granted the waiver by the Pediatric Review Committee (PeRC) on September 1, 2010, because the proposed indications do not exist in children. A description of pediatric studies conducted under a Pediatric Written Request (PWR) appear in the Pediatric Use subsection of RLD (Gemzar) labeling. The Gemzar pediatric use information is protected by Pediatric Exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 17, 2013.

The Division of Drug Oncology Products (DDOP) consulted the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) on October 8, 2010, to determine whether protected pediatric use information that appears in Gemzar labeling can be carved-out of this 505(b)(2) gemcitabine labeling. DDOP believes a carve out of this information would not affect safe use of this product.

## **BACKGROUND**

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

Gemzar (gemcitabine) is currently approved in adult patients for use in the treatment of:

- ovarian cancer in combination with carboplatin;
- breast cancer in combination with paclitaxel;
- non-small cell lung cancer in combination with cisplatin; and
- pancreatic cancer as a single-agent

Gemzar is not approved for use in pediatric cancer patients; however, pediatric studies were conducted and Gemzar labeling contains information regarding safety, dosing (including dose-limiting toxicity), and lack of effectiveness in pediatric patients with refractory leukemia. The pediatric use information was added to labeling as a result of studies performed under the Best Pharmaceuticals for Children Act (BPCA).

FDA issued a Pediatric Written Request for gemcitabine on October 5, 2001, reissued July 3, 2002, and amended November 13, 2003, and July 9, 2004, for the following studies in children with cancer:

Phase 1: A dose-finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.

Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients with refractory ALL or AML or relapsed tumor(s). Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

Eli Lilly & Company submitted a supplemental application (NDA 20-509/S-033) on October 26, 2004 (received October 27, 2004), containing the pediatric study data conducted in response to the PWR. Efficacy was not demonstrated for the pediatric cancers studied. The pediatric maximum tolerated dose was determined and the toxicities observed were similar to those observed in adult patients. No unexpected safety concerns were observed.

Gemzar, NDA 20-509/S-033, was approved on April 26, 2005, and the labeling was revised to include the pediatric study data conducted in response to the PWR. Six months of Pediatric Exclusivity under BPCA (expires November 17, 2013) were granted to Eli Lilly & Company for Gemzar for fairly meeting the terms of the PWR.

### **Best Pharmaceuticals for Children Act of 2007**

The goal of both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to provide pediatric information in drug labeling to encourage the appropriate use of drugs in treating pediatric patients. BPCA [section 505A(o)(2)(A) and 505A(o)(2)(B) the Act] addresses the approval of generic drugs when pediatric information protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the innovator labeling so that when possible, innovator pediatric labeling will not block generics from entering the market. In summary, 1) when new pediatric information in labeling is protected by patent or exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] and “carved out,” a disclaimer is necessary; and, 2) important pediatric safety information, particularly if related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use) may be retained.

BPCA does not address the carve-out of protected pediatric information from 505(b)(2) product labeling; however, approval of a 505(b)(2) application may be delayed because of patent and exclusivity rights that apply to the listed drug (see 21 CFR 314.50(i), 314.107, 314.108, and section 505(A)(b)(B)(ii) of the Act.<sup>1</sup>

---

<sup>1</sup> See Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999

## **PEDIATRIC USE LABELING**

**Sponsor's Proposed Pediatric Use 505(b)(2) Gemcitabine Injection labeling (April, 2010)**

(b) (4)

### **Current Approved Pediatric Use Gemzar labeling (March 19, 2010)**

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

The safety and effectiveness of Gemzar in pediatric patients has not been established. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m<sup>2</sup>/min for 360 minutes three times weekly followed by a one-week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m<sup>2</sup>/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

### **DDOP Proposal for Pediatric Use 505(b)(2) Gemcitabine Injection Labeling**

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

The safety and effectiveness of gemcitabine in pediatric patients has not been established.

## **DISCUSSION AND CONCLUSIONS**

BPCA allows for the retention of protected pediatric use information in generic labeling if the information describes important pediatric safety information, particularly if it related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use). In this manner, when possible, pediatric labeling will not block generics from entering the market. However, when protected pediatric use information can be safely carved-out of generic labeling because the carve-out does not impact the safe use of the drug in pediatric

patients, a disclaimer for the carved-out information is required under BPCA. The disclaimer states that due to an innovator's marketing exclusivity, the pediatric use information does not appear in the generic labeling. The Office of Chief Counsel (OCC) must approve the language of disclaimers used when protected pediatric information is carved-out of generic labeling.

BPCA does not address the carve-out or retention of protected pediatric information from 505(b)(2) products, nor does BPCA address the use of disclaimers for protected pediatric use information that is carved-out of 505(b)(2) product labeling. If FDA determines that the protected pediatric information is important safety information; and therefore, must be retained in 505(b)(2) product labeling for reasons of safe use, then a full approval for the affected 505(b)(2) product cannot be issued until Pediatric Exclusivity has expired.

In the case of gemcitabine, pediatric use information was added to Gemzar (NDA 20-509/S-033) labeling on April 26, 2005 and six months of Pediatric Exclusivity was granted to Eli Lilly & Company for Gemzar for fairly meeting the terms of the PWR. Pediatric Exclusivity expires on November 17, 2013; therefore, the pediatric use information in Gemzar labeling is protected until the Pediatric Exclusivity expires. Although efficacy was not demonstrated with gemcitabine in pediatric cancer patients in studies conducted under the PWR; information was added to labeling regarding the maximum tolerated dose as well as lack of meaningful clinical activity. However, no unexpected safety concerns were seen and toxicities observed were similar to those observed in the adult population with this cytotoxic chemotherapeutic drug.

The Division of Drug Oncology Products (DDOP) recommends the carve-out of protected pediatric information from this 505(b)(2) gemcitabine labeling because the DDOP opinion is that the carve-out of this information is not expected to affect the safe use of the product, given that most children in the U.S. with cancer are treated on Children's Oncology Group (COG) treatment protocols. While this assumption is likely, the Sponsor has not submitted data to support the opinion that pediatric patients are treated outside of COG protocols. Gemcitabine has toxicities that were seen in pediatric clinical trials that were the same as the toxicities seen in adult clinical trials. Those toxicities are monitored routinely in patients receiving chemotherapy, and are not unique to gemcitabine or use of gemcitabine in the pediatric population. Because gemcitabine is not labeled for use in the pediatric population and there is nothing unique that would create a safety concern for pediatric patients administered this product off label through COG protocols, there does not appear to be potential for harm if the protected pediatric information is omitted from labeling.

Although not the situation with gemcitabine, when there is a pediatric safety concern conveyed in protected labeling, and where omitting the information may lead to harm, PMHS believes that the FDA has the authority to require that the information remain in labeling, and thus approval of a 505(b)(2) product must wait for expiration of the protections to be approved.

The Agency has been implementing pediatric legislation for over 10 years. This legislation was passed because of the lack of pediatric data in labeling. The legislation provides for a carve-out of protected information in generic products' labeling, when removing this

information will not affect the safe use of a product, because generic drugs are generally more affordable, and allowing a carve-out serves a public health need. 505(b)(2) products do not serve a public health need, and are often not any cheaper than the innovator. With the approval of 505(b)(2) gemcitabine products, only the innovator gemcitabine product will include pediatric data in labeling (data which was made available at a cost to the U.S. government and thus taxpayers, based on exclusivity granted). Despite the fact that PMHS believes this approach is not consistent with the intent of BPCA, the legislation does not provide the FDA with the authority to carve-out language and add a disclaimer for applications other than 505(j)s. Therefore, a 505(b)(2) product can simply omit protected pediatric information and not contain a disclaimer.

## **RECOMMENDATIONS**

PMHS would prefer that all drugs with data on the safe and effective use in the pediatric population be labeled with such information, especially when that information was obtained under legislation intended to provide evidence based labeling. However, because the pediatric legislation did not anticipate the conditions of 505(b)(2) applications, and because the pediatric data in gemcitabine labeling does not pose a tangible safety risk if omitted, DDOP can decide to omit the protected pediatric information and approve this 505(b)(2) gemcitabine application. The following pediatric use statement proposed by DDOP, while not optimum, is accurate for this 505(b)(2) gemcitabine product labeling:

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

The safety and effectiveness of gemcitabine in pediatric patients have not been established.

---

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

JEANINE A BEST  
11/16/2010

HARI C SACHS  
11/16/2010

LISA L MATHIS  
11/17/2010