CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078815

Name: Oxaliplatin for Injection (Preservative-Free)
50 mg/vial and 100 mg/vial
Single-Use Vials

Sponsor: Hospira Worldwide Inc.

Approval Date: September 30, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-815

Hospira Worldwide Inc.
Attention: Laurie Wojtko
Senior Associate, Global Regulatory Affairs
Department 389, Bldg H2-2
275 North Field Drive
Lake Forest, IL 60045

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 9, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxaliplatin for Injection, (Preservative-Free), 50 mg/vial and 100 mg/vial, Single-use Vials.

Reference is also made to the tentative approval letter issued by this office on May 22, 2009, and to your amendment dated September 3, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Eloxatin for Injection, 50 mg/vial and 100 mg/vial, respectively, of Sanofi Aventis US, LLC (Sanofi).

The RLD upon which you have based your ANDA, Sanofi's Eloxatin for Injection, 50 mg/vial and 100 mg/vial, is subject to periods of patent protection. The following patents and their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,290,961 (the '961 patent)	July 12, 2013
5,338,874 (the '874 patent)	October 7, 2013
5,420,319 (the '319 patent)	February 9, 2017

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Hospira Worldwide PTY (Hospira) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. You have notified the agency that Hospira complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '874 patent was brought against Hospira within the statutory 45-day period in the United States District Court for the District of New Jersey [Sanofi-Aventis U.S. LLC v. Mayne Pharma Limited, Civil Action No. 3:07-CV-03409-FLW-JJH]. You have also notified the agency that on June 30, 2009, the court decided that the '874 patent is invalid, unenforceable, or not infringed; therefore, under section 505(j)(5)(B)(iii) of the Act, your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, we note that Hospira was one of the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification to the patents listed above. Therefore, with this approval, Hospira is eligible for 180 days of generic drug exclusivity for Oxaliplatin for Injection, 50 mg and 100 mg Single-use Vials. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, begins to run from the date of commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence - SPL for Approved ANDA 78-815".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78815	ORIG-1	HOSPIRA WORLDWIDE INC	OXALIPLATIN

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

/s/

ROBERT L WEST
09/30/2009
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-815

Hospira Worldwide PTY
Attention: Laurie Wojtko
Senior Associate, Global Regulatory Affairs
275 North Field Drive
D-0389, Bldg H2-2N
Lake Forest, IL 60045

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 9, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial Single-dose Vials.

Reference is also made to your amendments dated August 23, 2007; August 1, September 4, November 3, 14 and 19, 2008; and February 3 and 5, and April 29, 2009. In addition, we acknowledge receipt of your correspondence dated August 7, and September 10, 2007, addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Eloxatin for Injection, 50 mg/vial and 100 mg/vial, of Sanofi Synthelabo, Inc., is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the

agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
5,290,961 (the '961 patent)	July 12, 2013
5,338,874 (the '874 patent)	October 7, 2013
5,420,319 (the '319 patent)	February 9, 2017

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Hospira Worldwide PTY (Hospira) for infringement of one or more of the patents that were the subject of the paragraph IV certifications. You have notified the agency that Hospira complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '874 patent was brought against Hospira in the United States District Court for the District of New Jersey [Sanofi-Aventis U.S. LLC v. Mayne Pharma Limited, Civil Action No. 3:07-CV-03409-FLW-JJH].

Therefore, final approval cannot be granted until:

1. a. pursuant to sections 505(j)(5)(B)(iii)[1], 505(j)(5)(F)(ii), and 505A(b)(1)(A)(i) of the Act, the expiration of the 8-year period from the date of approval of the RLD,

   b. the date the court decides[2] that the '874 patent is invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

[1] Because information on the '874 patent was submitted before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted. See MMA § 1101(c)(3).

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

c. the ‘874 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your ANDA prior to final approval, please submit a “MINOR AMENDMENT – FINAL APPROVAL REQUESTED” 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either “major” or “minor” changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the “Orange Book.”

For further information on the status of this application, or prior to submitting additional amendments, please contact Esther Chuh, Project Manager, at 240-276-8530.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
5/22/2009 02:11:40 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Oxaliplatin for Injection safely and effectively. See full prescribing information for Oxaliplatin for Injection.

Oxaliplatin for Injection, powder for solution for intravenous use

Initial U.S. Approval: 2002

WARNING: ANAPHYLACTIC REACTIONS
See full prescribing information for complete boxed warning.
Anaphylactic reactions to Oxaliplatin for Injection have been reported, and may occur within minutes of Oxaliplatin for Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms. (5.1)

------------------------------------ INDICATIONS AND USAGE --------------------------------------

Oxaliplatin for Injection is a platinum-based drug used in combination with infusional 5-fluorouracil/leucovorin, which is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.
- treatment of advanced colorectal cancer. (1)

-------------------------------- DOSAGE AND ADMINISTRATION ----------------------------------

- Administer Oxaliplatin for Injection in combination with 5-fluorouracil/leucovorin every 2 weeks. (2.1):
  - Day 1: Oxaliplatin for Injection 85 mg/m² intravenous infusion in 250-500 mL 5% Dextrose Injection, USP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose Injection, USP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.
  - Day 2: leucovorin 200 mg/m² intravenous infusion over 120 minutes followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.
- Reduce the dose of Oxaliplatin for Injection to 75 mg/m² (adjuvant setting) or 65 mg/m² (advanced colorectal cancer) (2.2):
  - if there are persistent grade 2 neurosensory events that do not resolve.
  - after recovery from grade 3/4 gastrointestinal toxicities (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. Delay next dose until neutrophils ≥ 1.5 x 10⁹/L and platelets ≥ 75 x 10⁹/L.
- Discontinue Oxaliplatin for Injection if there are persistent Grade 3 neurosensory events. (2.2)
- Never reconstitute or prepare final dilution with a sodium chloride solution or other chloride-containing solutions. (2.3)

------------------------------ DOSAGE FORMS AND STRENGTHS --------------------------------

Single use vials of 50 mg or 100 mg oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. (3)

--------------------------------------- CONTRAINDICATIONS ---------------------------------------

- Known allergy to Oxaliplatin for Injection or other platinum compounds. (4, 5.1)

--------------------------------- WARNINGS AND PRECAUTIONS ---------------------------------

- Allergic Reactions: Monitor for development of rash, urticaria, erythema, pruritis, bronchospasm, and hypotension. (5.1)
- Neuropathy: Reduce the dose or discontinue Oxaliplatin for Injection if necessary. (5.2)
- Pulmonary Toxicity: May need to discontinue Oxaliplatin for Injection until interstitial lung disease or pulmonary fibrosis are excluded. (5.3)
- Hepatotoxicity: Monitor liver function tests. (5.4)
- Pregnancy. Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.5, 8.1)

-- ADVERSE REACTIONS --

Most common adverse reactions (incidence ≥ 40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. Other adverse reactions, including serious adverse reactions, have been reported. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: [04/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLACTIC REACTIONS

Anaphylactic reactions to Oxaliplatin for Injection have been reported, and may occur within minutes of Oxaliplatin for Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Oxaliplatin for Injection, used in combination with infusional 5-fluorouracil/leucovorin, is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.
- treatment of advanced colorectal cancer.

2 DOSAGE and ADMINISTRATION

Oxaliplatin for Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

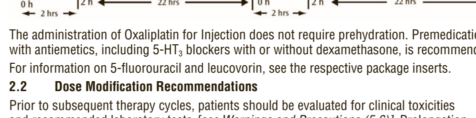
2.1 Dosage

Administer Oxaliplatin for Injection in combination with 5-fluorouracil/leucovorin every 2 weeks. For advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles):

Day 1: Oxaliplatin for Injection 85 mg/m² intravenous infusion in 250-500 mL 5% Dextrose injection, USP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose Injection, USP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Day 2: Leucovorin 200 mg/m² intravenous infusion over 120 minutes, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Figure 1



The administration of Oxaliplatin for Injection does not require prehydration. Premedication with antiemetics, including 5-HT_3 blockers with or without dexamethasone, is recommended.

For information on 5-fluorouracil and leucovorin, see the respective package inserts.

2.2 Dose Modification Recommendations

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests *[see Warnings and Precautions (5.6)]*. Prolongation of infusion time for Oxaliplatin for Injection from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-fluorouracil and leucovorin do not need to be changed.

Adjuvant Therapy in Patients with Stage III Colon Cancer

Neuropathy and other toxicities were graded using the NCI CTC scale version 1 *[see Warnings and Precautions (5.2)]*.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin for Injection to 75 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin for Injection to 75 mg/m² and infusional 5-fluorouracil to 300 mg/m² bolus and 500 mg/m² 22 hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥ 1.5 x 10⁹/L and platelets ≥ 75 x 10⁹/L.

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

Neuropathy was graded using a study-specific neurotoxicity scale *[see Warnings and Precautions (5.2)]*. Other toxicities were graded by the NCI CTC, Version 2.0.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin for Injection to 65 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin for Injection to 65 mg/m² and 5-fluorouracil by 20% (300 mg/m² bolus and 500 mg/m² 22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥ 1.5 x 10⁹/L and platelets ≥ 75 x 10⁹/L.

2.3 Preparation of Infusion Solution

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. **Do not administer the reconstituted solution without further dilution.** The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F] or up to 24 hours under refrigeration [2-8°C (36-46°F)]**.

Oxaliplatin for Injection is not light sensitive.

Oxaliplatin for Injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. **The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with Oxaliplatin for Injection should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

3 DOSAGE FORMS AND STRENGTHS

Oxaliplatin for Injection is supplied in single-use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution.

4 CONTRAINDICATIONS

Oxaliplatin for Injection should not be administered to patients with a history of known allergy to Oxaliplatin for Injection or other platinum compounds *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

See boxed warning

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to Oxaliplatin for Injection has been observed in 2 to 3% of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

5.2 Neuropathy

Oxaliplatin for Injection is associated with two types of neuropathy:

An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received Oxaliplatin for Injection with 5-fluorouracil/leucovorin. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the Oxaliplatin for Injection with 5-fluorouracil/leucovorin combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1 to 2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin for Injection because cold temperature can exacerbate acute neurological symptoms.

A persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving Oxaliplatin for Injection with 5-fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of Oxaliplatin for Injection.

In the adjuvant colon cancer trial, neuropathy was graded using a prelisted module derived from the Neuro-Sensory section of the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale, Version 1, as follows:

Table 1 - NCI CTC Grading for Neuropathy in Adjuvant Patients

Grade	Definition
Grade 0	No change or none
Grade 1	Mild paresthesias, loss of deep tendon reflexes
Grade 2	Mild or moderate objective sensory loss, moderate paresthesias
Grade 3	Severe objective sensory loss or paresthesias that interfere with function
Grade 4	Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the Oxaliplatin for Injection combination with a frequency of 92% (all grades) and 13% (grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had any grade (Grade 1=40%, Grade 2=16%, Grade 3=5%) peripheral sensory neuropathy decreasing to 39% at 6 months follow-up (Grade 1=31%, Grade 2=7%, Grade 3=1%) and 21% at 18 months of follow-up (Grade 1=17%, Grade 2=3%, Grade 3=1%).

In the advanced colorectal cancer studies, neuropathy was graded using a study-specific neurotoxicity scale, which was different from the NCI CTC scale, Version 2.0 (see below).

Table 2 - Grading Scale for Paresthesias/Dysesthesias in Advanced Colorectal Cancer Patients

Grade	Definition
Grade 1	Resolved and did not interfere with functioning
Grade 2	Interfered with function but not daily activities
Grade 3	Pain or functional impairment that interfered with daily activities
Grade 4	Persistent impairment that is disabling or life-threatening

Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

5.3 Pulmonary Toxicity

Oxaliplatin for Injection has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the Oxaliplatin for Injection combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the Oxaliplatin for Injection plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, Oxaliplatin for Injection should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

5.4 Hepatotoxicity

Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the Oxaliplatin for Injection combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases *[see Clinical Trials Experience (6.1)]*.

5.5 Use in Pregnancy

Pregnancy Category D

Oxaliplatin for Injection may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin for Injection in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Oxaliplatin for Injection *[See Use in Specific Populations (8.1)]*.

5.6 Recommended Laboratory Tests

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each Oxaliplatin for Injection cycle *[see Dosage and Administration (2)]*.

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Oxaliplatin for Injection plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving Oxaliplatin for Injection plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities and hepatotoxicities can occur *[See Warnings and Precautions (5.1)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with advanced colorectal cancer have been treated in clinical studies with Oxaliplatin for Injection. The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea *[see Warnings and Precautions (5)]*.

Combination Adjuvant Therapy with Oxaliplatin for Injection and Infusional 5-fluorouracil/leucovorin in Patients with Colon Cancer

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with Oxaliplatin for Injection in combination with infusional 5-fluorouracil/leucovorin *[see Clinical Studies (14)]*. The incidence of grade 3 or 4 adverse reactions was 70% on the Oxaliplatin for Injection combination arm, and 31% on the infusional 5-fluorouracil/leucovorin arm. The adverse reactions in this trial are shown in the tables below. Discontinuation of treatment due to adverse reactions occurred in 15% of the patients receiving Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin. Both 5-fluorouracil/leucovorin and Oxaliplatin for Injection are associated with gastrointestinal or hematologic adverse reactions. When Oxaliplatin for Injection is administered in combination with infusional 5-fluorouracil/leucovorin, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6) in both the Oxaliplatin for Injection combination and infusional 5-fluorouracil/leucovorin arms, respectively. Deaths within 60 days from initiation of therapy were 0.3% (n=3) in both the Oxaliplatin for Injection combination and infusional 5-fluorouracil/leucovorin arms, respectively. On the Oxaliplatin for Injection combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracerebral bleeding and one from eosinophilic pneumonia. On the 5-fluorouracil/leucovorin arm, one death was due to suicide, 2 from Steven-Johnson Syndrome (1 patient also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction and 1 probable abdominal aorta rupture.

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥ 5% and for NCI grade 3/4 events with incidences ≥ 1%.

Table 3 - Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment (≥ 5% of all patients and with ≥ 1% NCI Grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=1108		5-FU/LV N=1111	
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection Site Reaction[1]	11	3	10	3
Gastrointestinal				
Nausea	74	5	61	2
Diarrhea	56	11	48	7
Vomiting	47	6	24	1
Stomatitis	42	3	40	2
Anorexia	13	1	8	<1
Fever/Infection				
Fever	27	1	12	1
Infection	25	4	25	3
Neurology				
Overall Peripheral Sensory Neuropathy	92	12	16	<1

[1]Includes thrombosis related to the catheter

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥ 5% but with incidences <1% NCI grade 3/4 events.

Table 4 - Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment (≥ 5% of all patients, but with <1% NCI Grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=1108	5-FU/LV N=1111
Adverse Reactions (WHO/Pref)	**All Grades (%)**	**All Grades (%)**
Allergy/Immunology		
Rhinitis	6	8
Constitutional Symptoms/Pain/Ocular/Visual		
Epistaxis	16	12
Weight Increase	10	10
Conjunctivitis	9	15
Headache	7	5
Dyspnea	5	3
Pain	5	5
Lacrimation Abnormal	4	12
Dermatology/Skin		
Alopecia	30	28
Gastrointestinal		
Constipation	22	19
Taste Perversion	12	8
Dyspepsia	8	5
Metabolic		
Phosphate Alkaline increased	42	20
Neurology		
Sensory Disturbance	8	1

Although specific events can vary, the overall frequency of adverse reactions was similar in men and women and in patients <65 and ≥ 65 years. However, the following grade 3/4 events were more common in females: diarrhea, fatigue, granulocytopenia, nausea and vomiting. In patients ≥ 65 years old, the incidence of grade 3/4 diarrhea and granulocytopenia was higher than in younger patients. Insufficient subgroup sizes prevented analysis of safety by race. The following additional adverse reactions, were reported in ≥ 2% and <5% of the patients in the Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): pain, leukopenia, weight decrease, coughing.

The number of patients who developed secondary malignancies was similar; 62 in the Oxaliplatin for Injection combination arm and 68 in the infusional 5-fluorouracil/leucovorin arm. An exploratory analysis showed that the number of deaths due to secondary malignancies was 1.96% in the Oxaliplatin for Injection combination arm and 0.98% in infusional 5-fluorouracil/leucovorin arm. In addition, the number of cardiovascular deaths was 1.4% in the Oxaliplatin for Injection combination arm as compared to 0.7% in the infusional 5-fluorouracil/leucovorin arm. Clinical significance of these findings is unknown.

Patients Previously Untreated for Advanced Colorectal Cancer

Two hundred and fifty-nine patients were treated in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm of the randomized trial in patients previously untreated for advanced colorectal cancer *[see Clinical Studies (14)]*. The adverse reaction profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown in the tables below.

Both 5-fluorouracil and Oxaliplatin for Injection are associated with gastrointestinal and hematologic adverse reactions. When Oxaliplatin for Injection is administered in combination with 5-fluorouracil, the incidence of these events is increased.

The incidence of death within 30 days of treatment in the previously untreated for advanced colorectal cancer study, regardless of causality, was 3% with the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination, 5% with irinotecan plus 5-fluorouracil/leucovorin, and 3% with Oxaliplatin for Injection plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination, 5.1% with irinotecan plus 5-fluorouracil/leucovorin, and 3.1% with Oxaliplatin for Injection plus irinotecan. The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥ 5% and for grade 3/4 events with incidences ≥ 1%.

Table 5 – Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (≥ 5% of all patients and with ≥ 1% NCI Grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=259		irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	99	82	98	70	99	76
Allergy/Immunology						
Hypersensitivity	12	2	5	0	6	1
Cardiovascular						
Thrombosis	6	5	6	6	3	3
Hypotension	5	3	6	3	4	3
Constitutional Symptoms/Pain/Ocular/Visual						
Fatigue	70	7	58	11	66	16
Abdominal Pain	29	8	31	7	39	10
Myalgia	14	2	6	0	9	2
Pain	7	1	5	1	6	1
Vision abnormal	5	0	2	1	6	1
Neuralgia	5	0	0	0	2	1
Dermatology/Skin						
Skin reaction – hand/foot	7	1	2	1	1	0
Injection site reaction	6	0	1	0	4	1
Gastrointestinal						
Nausea	71	6	67	15	83	19
Diarrhea	56	12	65	29	76	25
Vomiting	41	4	43	13	64	23
Stomatitis	38	0	25	1	19	1
Anorexia	35	2	25	4	27	5
Constipation	32	4	27	2	21	2
Diarrhea-colostomy	13	2	16	7	16	3
Gastrointestinal NOS*	5	2	4	2	3	2
Hematology/Infection						
Infection normal ANC**	10	4	5	1	7	2
Infection low ANC**	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Febrile neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	6	2
Dehydration	9	5	16	11	14	7
Hypoalbuminemia	8	0	5	2	9	1
Hyponatremia	8	2	7	4	4	1
Urinary frequency	5	1	2	1	3	1
Neurology						
Overall Neuropathy	82	19	18	2	69	7
Paresthesias	77	18	16	2	62	6
Pharyngo-laryngeal dysesthesias	38	2	1	0	28	1
Neuro-sensory	12	1	2	0	9	1
Neuro NOS*	1	0	1	0	1	0
Pulmonary						
Cough	35	1	25	2	17	1
Dyspnea	18	7	14	3	11	2
Hiccups	5	1	2	0	3	2

* Not otherwise specified
** Absolute neutrophil count

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥ 5% but with incidences <1% NCI Grade 3/4 events.

Table 6 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (≥ 5% of all patients but with < 1% NCI Grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=259	irinotecan + 5-FU/LV N=256	Oxaliplatin + irinotecan N=258
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**All Grades (%)**	**All Grades (%)**
Allergy/Immunology			
Rash	11	4	7
Rhinitis allergic	10	6	6
Cardiovascular			
Edema	15	13	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	13	6	9
Weight loss	11	9	11
Epistaxis	10	2	2
Tearing	9	1	2
Rigors	8	2	7
Dysphasia	5	3	3
Sweating	5	6	12
Arthralgia	5	5	8
Dermatology/Skin			
Alopecia	38	44	67
Flushing	7	2	5
Pruritis	6	4	2
Dry Skin	6	2	5
Gastrointestinal			
Taste perversion	14	6	8
Dyspepsia	12	7	5
Flatulence	9	6	5
Mouth Dryness	5	2	3
Hematology/Infection			
Fever normal ANC*	16	9	9
Hepatic/Metabolic/Laboratory/Renal			
Hypocalcemia	7	5	4
Elevated Creatinine	4	4	5
Neurology			
Insomnia	13	9	11
Depression	9	5	7
Dizziness	8	6	10
Anxiety	5	2	6

* Absolute neutrophil count

Adverse reactions were similar in men and women and in patients <65 and ≥ 65 years, but older patients may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope. The following additional adverse reactions, at least possibly related to treatment and potentially important, were reported in ≥ 2% and <5% of the patients in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): metabolic, pneumonitis, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nail changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone pain, pigmentation changes, and urticaria.

Previously Treated Patients with Advanced Colorectal Cancer

Four hundred and fifty patients (about 150 receiving the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin) were studied in a randomized trial in patients with refractory and relapsed colorectal cancer *[see Clinical Studies (14)]*. The adverse reaction profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown in the tables below. Thirteen percent of patients in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm and 18% in the 5-fluorouracil/leucovorin arm of the previously treated study had to discontinue treatment because of adverse effects related to gastrointestinal, or hematologic adverse reactions, or neuropathies. Both 5-fluorouracil and Oxaliplatin for Injection are associated with gastrointestinal and hematologic adverse reactions. When Oxaliplatin for Injection is administered in combination with 5-fluorouracil, the incidence of these events is increased.

The incidence of death within 30 days of treatment in the previously treated study, regardless of causality, was 5% with the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination, 8% with Oxaliplatin for Injection alone, and 7% with 5-fluorouracil/leucovorin. Of the 7 deaths that occurred on the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm within 30 days of stopping treatment, 3 may have been treatment related, associated with gastrointestinal bleeding or dehydration.

The following table provides adverse reactions reported in the previously treated study *[see Clinical Studies (14)]* by body system and in decreasing order of frequency in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥ 5% and for grade 3/4 events with incidences ≥ 1%. This table does not include hematologic and blood chemistry abnormalities; these are shown separately below.

Table 7 – Adverse Reactions Reported In Previously Treated Colorectal Cancer Clinical Trial (≥ 5% of all patients and with ≥ 1% NCI Grade 3/4 events)

	5-FU/LV (N = 142)		Oxaliplatin (N = 153)		Oxaliplatin + 5-FU/LV (N = 150)	
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	98	41	100	46	99	73
Cardiovascular						
Dyspnea	11	2	13	7	20	4
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Thromboembolism	4	2	2	1	9	8
Chest Pain	4	1	5	1	8	1
Constitutional Symptoms/Pain						
Fatigue	52	6	61	9	68	7
Back Pain	16	4	11	0	19	3
Pain	9	3	14	3	15	2
Dermatology/Skin						
Injection Site Reaction	5	1	9	0	10	3
Gastrointestinal						
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdominal Pain	31	5	31	7	33	4
Anorexia	20	1	20	2	29	3
Gastroesophageal Reflux	3	0	1	0	5	2
Hematology/Infection						
Fever	23	1	25	1	29	1
Febrile Neutropenia	1	1	0	0	6	6
Hepatic/Metabolic/Laboratory/Renal						
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Neurology						
Neuropathy	17	0	76	7	74	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6

The following table provides adverse reactions reported in the previously treated study *[see Clinical Studies (14)]* by body system and in decreasing order of frequency in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥ 5% but with incidences <1% NCI Grade 3/4 events.

Table 8 - Adverse Reactions Reported In Previously Treated Colorectal Cancer Clinical Trial (≥ 5% of all patients but with < 1% NCI Grade 3/4 events)

	5-FU/LV (N = 142)	Oxaliplatin (N = 153)	Oxaliplatin + 5-FU/LV (N = 150)
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**All Grades (%)**	**All Grades (%)**
Allergy/Immunology			
Rhinitis	4	6	15
Allergic Reaction	1	3	10
Rash	5	5	9
Cardiovascular			
Peripheral Edema	11	5	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	8	13	17
Arthralgia	10	7	10
Epistaxis	1	2	9
Abnormal Lacrimation	6	1	7
Rigors	6	9	7
Dermatology/Skin			
Hand-Foot Syndrome	13	1	11
Flushing	2	3	10
Alopecia	3	3	7
Gastrointestinal			
Constipation	23	31	32
Dyspepsia	10	7	14
Taste Perversion	1	5	13
Mucositis	10	2	7
Flatulence	6	3	5
Hepatic/Metabolic/Laboratory/Renal			
Hematuria	4	0	6
Dysuria	1	1	6
Neurology			
Dizziness	8	7	13
Insomnia	4	11	9
Pulmonary			
Upper Resp Tract Infection	4	7	10
Pharyngitis	10	2	9
Hiccup	0	2	5

Adverse reactions were similar in men and women and in patients <65 and ≥ 65 years, but older patients may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue. The following additional adverse reactions, at least possibly related to treatment and potentially important, were reported in ≥ 2% and <5% of the patients in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritus, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

Hematologic Changes

The following tables list the hematologic changes occurring in ≥ 5% of patients, based on laboratory values and NCI grade, with the exception of those events occurring in adjuvant patients and anemia in the patients previously untreated for advanced colorectal cancer, respectively, which are based on AE reporting and NCI grade alone.

Table 9 - Adverse Hematologic Reactions in Patients with Colon Cancer Receiving Adjuvant Therapy (≥ 5% of patients)

Hematology Parameter	Oxaliplatin + 5-FU/LV (N=1108)		5-FU/LV (N=1111)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	76	1	67	<1
Neutropenia	79	41	40	5
Thrombocytopenia	77	2	19	<1

Table 10 – Adverse Hematologic Reactions in Patients Previously Untreated for Advanced Colorectal Cancer (≥ 5% of patients)

Hematology Parameter	Oxaliplatin + 5-FU/LV N=259		irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	27	3	28	4	25	3
Leukopenia	85	20	84	23	76	24
Neutropenia	81	53	77	44	71	36
Thrombocytopenia	71	5	26	2	44	4

Table 11 – Adverse Hematologic Reactions in Previously Treated Patients (≥ 5% of patients)

Hematology Parameter	5-FU/LV (N=142)		Oxaliplatin (N=153)		Oxaliplatin + 5-FU/LV (N=150)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	68	2	64	1	81	2
Leukopenia	34	1	13	0	76	19
Neutropenia	25	5	7	0	73	44
Thrombocytopenia	20	0	30	3	64	4

Thrombocytopenia and Bleeding

Thrombocytopenia was frequently reported with the combination of Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin. The incidence of all hemorrhagic events in the adjuvant and previously treated patients was higher on the Oxaliplatin for Injection combination arm compared to the infusional 5-fluorouracil/leucovorin arm. These events included gastrointestinal bleeding, hematuria, and epistaxis. In the adjuvant trial, two patients died from intracerebral hemorrhages.

The incidence of Grade 3/4 thrombocytopenia was 2% in adjuvant patients with colon cancer. In patients treated for advanced colorectal cancer the incidence of Grade 3/4 thrombocytopenia was 3 to 5%, and the incidence of these events was greater for the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin over the irinotecan plus 5-fluorouracil/leucovorin or 5-fluorouracil/leucovorin control groups. Grade 3/4 gastrointestinal bleeding was reported in 0.2% of adjuvant patients receiving Oxaliplatin for Injection and 5-fluorouracil/leucovorin. In the previously untreated patients, the incidence of epistaxis was 10% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin arm, and 2% and 1%, respectively, in the irinotecan plus 5-fluorouracil/leucovorin or irinotecan plus Oxaliplatin for Injection arms.

Neutropenia

Neutropenia was frequently observed with the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, with Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer, respectively. In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis. Grade 3 and 4 events were reported in 35% and 18% of the patients previously untreated for advanced colorectal cancer, respectively. Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respectively. In adjuvant patients the incidence of either febrile neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was 1.8% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin arm. The incidence of febrile neutropenia in the patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the irinotecan plus 5-fluorouracil/leucovorin arm and 4% (less than 1% of cycles) in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm. Additionally, in this same population, infection with grade 3 or 4 neutropenia was 12% in the irinotecan plus 5-fluorouracil/leucovorin, and 8% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination. The incidence of febrile neutropenia in the previously treated patients was 1% in the 5-fluorouracil/leucovorin arm and 6% (less than 1% of cycles) in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm.

Gastrointestinal

In patients receiving the combination of Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin for adjuvant treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those receiving infusional 5-fluorouracil/leucovorin alone (see table). In patients previously untreated for advanced colorectal cancer receiving the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, the incidence of Grade 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5-fluorouracil/leucovorin controls (see table). In previously treated patients receiving the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5-fluorouracil/leucovorin controls (see table).

The incidence of gastrointestinal adverse reactions in the previously untreated and previously treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-HT_3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of Oxaliplatin for Injection to 5-fluorouracil/leucovorin, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin for Injection.

Dermatologic

Oxaliplatin for Injection did not increase the incidence of alopecia compared to 5-fluorouracil/leucovorin alone. No complete alopecia was reported. The incidence of Grade 3/4 skin disorders was 2% in both the Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin and the infusional 5-fluorouracil/leucovorin alone arms in the adjuvant colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for advanced colorectal cancer was 2% in the irinotecan plus 5-fluorouracil/leucovorin arm and 7% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm. The incidence of hand-foot syndrome in previously treated patients was 13% in the 5-fluorouracil/leucovorin arm and 11% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm.

Intravenous Site Reactions

Extravasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain, has been reported.

Anticoagulation and Hemorrhage

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Oxaliplatin for Injection plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving Oxaliplatin for Injection plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

Renal

About 5 to 10% of patients in all groups had some degree of elevation of serum creatinine. The incidence of Grade 3/4 elevations in serum creatinine in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm was 1% in the previously treated patients. Serum creatinine measurements were not reported in the adjuvant trial.

Hepatic

Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to Oxaliplatin for Injection combination therapy *[see Warnings and Precautions (5.4)]*. The following tables list the clinical chemistry changes associated with hepatic toxicity occurring in ≥ 5% of patients, based on adverse reactions reported and NCI CTC grade for adjuvant patients and patients previously untreated for advanced colorectal cancer, laboratory values and NCI CTC grade for previously treated patients.

Table 12 - Adverse Hepatic Reactions in Patients with Stage II or III Colon Cancer Receiving Adjuvant Therapy (≥ 5% of patients)

Hepatic Parameter	Oxaliplatin + 5-FU/LV (N=1108)		5-FU/LV (N=1111)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Increase in transaminases	57	2	34	1
ALP increased	42	<1	20	<1
Bilirubinaemia	20	4	20	5

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Designer/Artworker (b) (6)
Date: 08/04/09
Version: 4

Table 13 – Adverse Hepatic – Clinical Chemistry Abnormalities in Patients Previously Untreated for Advanced Colorectal Cancer (≥ 5% of patients)

Clinical Chemistry	Oxaliplatin + 5-FU/LV N=259		irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
ALT (SGPT-ALAT)	6	1	2	0	5	2
AST (SGOT-ASAT)	17	1	2	1	11	1
Alkaline Phosphatase	16	0	8	0	14	2
Total Bilirubin	6	1	3	1	3	2

Table 14 – Adverse Hepatic – Clinical Chemistry Abnormalities in Previously Treated Patients (≥ 5% of patients)

Clinical Chemistry	5-FU/LV (N=142)		Oxaliplatin (N=153)		Oxaliplatin + 5-FU/LV (N=150)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
ALT (SGPT-ALAT)	28	3	36	1	31	0
AST (SGOT-ASAT)	39	2	54	4	47	0
Total Bilirubin	22	6	13	5	13	1

Thromboembolism

The incidence of thromboembolic events in adjuvant patients with colon cancer was 6% (1.8% grade 3/4) in the infusional 5-fluorouracil/leucovorin arm and 6% (1.2% grade 3/4) in the Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin combined arm, respectively. The incidence was 6 and 9% of the patients previously untreated for advanced colorectal cancer and previously treated patients in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Oxaliplatin for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole:

angioedema, anaphylactic shock

Central and peripheral nervous system disorders:

loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies, fasciculations, convulsion

Liver and Gastrointestinal system disorders:

severe diarrhea/vomiting resulting in hypokalemia, colitis (including *Clostridium difficile* diarrhea), metabolic acidosis; ileus; intestinal obstruction, pancreatitis; veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress.

Hearing and vestibular system disorders:

deafness

Platelet, bleeding, and clotting disorders:

immuno-allergic thrombocytopenia

prolongation of prothrombin time and of INR in patients receiving anticoagulants

Red Blood Cell disorders:

hemolytic uremic syndrome, immuno-allergic hemolytic anemia

Renal disorders:

Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Respiratory system disorders:

pulmonary fibrosis, and other interstitial lung diseases (sometimes fatal)

Vision disorders:

decrease of visual acuity, visual field disturbance, optic neuritis and transient vision loss (reversible following therapy discontinuation)

7 DRUG INTERACTIONS

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m^2 Oxaliplatin for Injection and 5-fluorouracil/leucovorin has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 Oxaliplatin for Injection dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Based on direct interaction with DNA, Oxaliplatin for Injection may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin for Injection in pregnant women. Reproductive toxicity studies in rats demonstrated adverse effects on fertility and embryo-fetal development at maternal doses that were below the recommended human dose based on body surface area. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant and use effective contraception while receiving treatment with Oxaliplatin for Injection.

Pregnant rats were administered oxaliplatin at less than one-tenth the recommended human dose based on body surface area during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during organogenesis). Oxaliplatin caused developmental mortality (increased early resorptions) when administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6-10. Administration of oxaliplatin to male and female rats prior to mating resulted in 97% post-implantation loss in animals that received approximately one-seventh the recommended human dose based on the body surface area.

8.3 Nursing Mothers

It is not known whether Oxaliplatin for Injection or its derivatives are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Oxaliplatin for Injection, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The effectiveness of oxaliplatin in children has not been established. Information related to the treatment of pediatric patients is approved for Sanofi-Aventis' Oxaliplatin for Injection drug product.

8.5 Geriatric Use

No significant effect of age on the clearance of ultrafilterable platinum has been observed.

In the adjuvant therapy colon cancer randomized clinical trial, *[see Clinical Studies (14)]* 723 patients treated with Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin were <65 years and 400 patients were ≥ 65 years. A descriptive subgroup analysis demonstrated that the improvement in DFS for the Oxaliplatin for Injection combination arm compared to the infusional 5-fluorouracil/leucovorin alone arm appeared to be maintained across genders. The effect of Oxaliplatin for Injection in patients ≥ 65 years of age was not conclusive. Insufficient subgroup sizes prevented analysis by race. Patients ≥ 65 years of age receiving the Oxaliplatin for Injection combination therapy experienced more grade 3-4 granulocytopenia than patients < 65 years of age (43% versus 39%).

In the previously untreated for advanced colorectal cancer randomized clinical trial *[see Clinical Studies (14)]* of Oxaliplatin for Injection, 160 patients treated with Oxaliplatin for Injection and 5-fluorouracil/leucovorin were <65 years and 99 patients were ≥ 65 years. The same efficacy improvements in response rate, time to tumor progression, and overall survival were observed in the ≥ 65 year old patients as in the overall study population. In the previously treated for advanced colorectal cancer randomized clinical trial *[see Clinical Studies (14)]* of Oxaliplatin for Injection, 95 patients treated with Oxaliplatin for Injection and 5-fluorouracil/leucovorin were <65 years and 55 patients were ≥ 65 years. The rates of overall adverse reactions, including grade 3 and 4 events, were similar across and within arms in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were higher in patients ≥ 65 years old. No adjustment to starting dose was required in patients ≥ 65 years old.

8.6 Patients with Renal Impairment

The safety and effectiveness of the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin in patients with renal impairment have not been evaluated. The combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

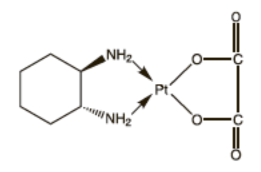
There is no known antidote for Oxaliplatin for Injection overdose. In addition to thrombocytopenia, the anticipated complications of an Oxaliplatin for Injection overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity.

Several cases of overdoses have been reported with Oxaliplatin for Injection. Adverse reactions observed were Grade 4 thrombocytopenia (< 25,000/mm^3) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial muscle spasms, gastrointestinal disorders such as nausea, vomiting, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death.

Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered. The maximum dose of oxaliplatin that has been administered in a single infusion is 825 mg.

11 DESCRIPTION

Oxaliplatin for Injection is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of *cis*-[(1 *R*,2 *R*)-1,2-cyclohexanediamine-*N,N'*] [oxalato(2-)-*O,O'*] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2- diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.



The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone. Oxaliplatin for Injection is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the *N7* positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific. *In vivo* studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil (5-FU), oxaliplatin exhibits *in vitro* and *in vivo* antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

12.3 Pharmacokinetics

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$; 0.43 hours and $t_{1/2\beta}$; 16.8 hours) and a long terminal elimination phase ($t_{1/2\gamma}$; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of Oxaliplatin for Injection at a dose of 85 mg/m^2 expressed as ultrafilterable platinum were Cmax of 0.814 mcg/mL and volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC_{0-48hr}) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

Distribution

At the end of a 2-hour infusion of Oxaliplatin for Injection, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks.

Metabolism

Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism *in vitro*.

Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species.

Elimination

The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of Oxaliplatin for Injection, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 – 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with GFR.

Pharmacokinetics in Special Populations

Pediatric

[See Use In Specific Patient Populations (8.4)].

Renal Impairment

The AUC_{0-48hr} of platinum in the plasma ultrafiltrate increases as renal function decreases. The AUC_{0-48hr} of platinum in patients with mild (creatinine clearance, CL_{cr} 50 to 80 mL/min), moderate (CL_{cr} 30 to < 50 mL/min) and severe renal (CL_{cr} < 30 mL/min) impairment is increased by about 60, 140 and 190%, respectively, compared to patients with normal renal function (CL_{cr} > 80 mL/min) *[See Adverse Reactions (6), Drug Interactions (7) and Use In Specific Patient Populations (8.6)]*.

Drug - Drug Interactions

No pharmacokinetic interaction between 85 mg/m^2 of Oxaliplatin for Injection and infusional 5-fluorouracil has been observed in patients treated every 2 weeks, but increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 of Oxaliplatin for Injection administered every 3 weeks. *In vitro*, platinum was not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. *In vitro*, oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No P450-mediated drug-drug interactions are therefore anticipated in patients. Since platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. Oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells *in vitro* (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both *in vitro* (chromosome aberration in human lymphocytes) and *in vivo* (mouse bone marrow micronucleus assay).

In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (decreased fetal weight).

Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This daily dose is approximately one-sixth of the recommended human dose on a body surface area basis.

14 CLINICAL STUDIES

14.1 Combination Adjuvant Therapy with Oxaliplatin for Injection and Infusional 5-fluorouracil/leucovorin in Patients with Colon Cancer

An international, multicenter, randomized study compared the efficacy and evaluated the safety of Oxaliplatin for Injection in combination with an infusional schedule of 5-fluorouracil/leucovorin to infusional 5-fluorouracil/leucovorin alone, in patients with stage II (Dukes' B2) or III (Dukes' C) colon cancer who had undergone complete resection of the primary tumor. The primary objective of the study was to compare the 3-year disease-free survival (DFS) in patients receiving Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin to those receiving 5-fluorouracil/leucovorin alone. Patients were to be treated for a total of 6 months (i.e., 12 cycles). A total of 2246 patients were randomized; 1123 patients per study arm. Patients in the study had to be between 18 and 75 years of age, have histologically proven stage II (T_3-T_4 N0 M0; Dukes' B2) or III (any T $N_{1,2}$ M0; Dukes' C) colon carcinoma (with the inferior pole of the tumor above the peritoneal reflection, i.e., ≥ 15 cm from the anal margin) and undergone (within 7 weeks prior to randomization) complete resection of the primary tumor without gross or microscopic evidence of residual disease. Patients had to have had no prior chemotherapy, immunotherapy or radiotherapy, and have an ECOG performance status of 0,1, or 2 (KPS ≥ 60%), absolute neutrophil count (ANC) > 1.5x10^9/L, platelets ≥ 100x10^9/L, serum creatinine ≤ 1.25 x ULN total bilirubin < 2 x ULN, AST/ALT < 2 x ULN and carcino-embryogenic antigen (CEA) <10 ng/mL. Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were ineligible for this trial.

The following table shows the dosing regimens for the two arms of the study.

Table 15 - Dosing Regimens in Adjuvant Therapy Study

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (FOLFOX4) (N =1123)	Day 1: Oxaliplatin: 85 mg/m^2 (2-hour infusion) + LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks 12 cycles
5-FU/LV (N=1123)	Day 1: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks 12 cycles

The following tables show the baseline characteristics and dosing of the patient population entered into this study. The baseline characteristics were well balanced between arms.

Table 16 - Patient Characteristics in Adjuvant Therapy Study

	Oxaliplatin + Infusional 5-FU/LV N=1123	Infusional 5-FU/LV N=1123
Sex: Male (%)	56.1	52.4
Female (%)	43.9	47.6
Median age (years)	61.0	60.0
<65 years of age (%)	64.4	66.2
≥65 years of age (%)	35.6	33.8
Karnofsky Performance Status (KPS) (%)		
100	29.7	30.5
90	52.2	53.9
80	4.4	3.3
70	13.2	11.9
≤60	0.6	0.4
Primary site (%)		
Colon including cecum	54.6	54.4
Sigmoid	31.9	33.8
Recto sigmoid	12.9	10.9
Other including rectum	0.6	0.9
Bowel obstruction (%)		
Yes	17.9	19.3
Perforation (%)		
Yes	6.9	6.9
Stage at Randomization (%)		
II (T=3,4 N=0, M=0)	40.1	39.9
III (T=any, N=1,2, M=0)	59.6	59.3
IV (T=any, N=any, M=1)	0.4	0.8
Staging – T (%)		
T1	0.5	0.7
T2	4.5	4.8
T3	76.0	75.9
T4	19.0	18.5
Staging – N (%)		
N0	40.2	39.9
N1	39.4	39.4
N2	20.4	20.7
Staging – M (%)		
M1	0.4	0.8

Table 17 - Dosing in Adjuvant Therapy Study

	Oxaliplatin + Infusional 5-FU/LV N=1108	Infusional 5-FU/LV N=1111
Median Relative Dose Intensity (%)		
5-FU	84.4	97.7
Oxaliplatin for Injection	80.5	N/A
Median Number of Cycles	12	12
Median Number of cycles with Oxaliplatin for Injection	11	N/A

The following table and figures summarize the disease-free survival (DFS) results in the overall randomized population and in patients with stage II and III disease based on an ITT analysis. The median duration of follow-up was approximately 77 months.

Table 18 - Summary of DFS analysis - ITT analysis

Parameter	Oxaliplatin + Infusional 5-FU/LV	Infusional 5-FU/LV
Overall		
N	1123	1123
Number of events – relapse or death (%)	304 (27.1)	360 (32.1)
Disease-free survival % [95% CI]*	73.3 [70.7, 76.0]	67.4 [64.6, 70.2]
Hazard ratio [95% CI] **	0.80 [0.68, 0.93]	
Stratified Logrank test	p=0.003	
Stage III (Dukes' C)		
N	672	675
Number of events – relapse or death (%)	226 (33.6)	271 (40.1)
Disease-free survival % [95% CI] *	66.4 [62.7, 70.0]	58.9 [55.2, 62.7]
Hazard ratio [95% CI] **	0.78 [0.65, 0.93]	
Logrank test	p=0.005	
Stage II (Dukes' B2)		
N	451	448
Number of events – relapse or death (%)	78 (17.3)	89 (19.9)
Disease-free survival % [95% CI]*	83.7 [80.2, 87.1]	79.9 [76.2, 83.7]
Hazard ratio [95% CI] **	0.84 [0.62, 1.14]	
Logrank test	p=0.258	

Data cut off for disease free survival 1 June 2006
*Disease-free survival at 5 years
**A hazard ratio of less than 1.00 favors Oxaliplatin for Injection + Infusion 5-fluorouracil/leucovorin

In the overall and stage III colon cancer populations DFS was statistically significantly improved in the Oxaliplatin for Injection combination arm compared to infusional 5-fluorouracil/leucovorin alone. However a statistically significant improvement in DFS was not noted in Stage II patients.

Figure 2 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone for the overall population (ITT analysis).

Figure 3 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone in Stage III patients.

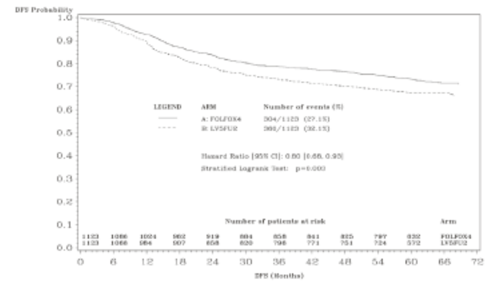


Figure 2 - DFS Kaplan-Meier curves by treatment arm (cutoff: 1 June 2006) – ITT population

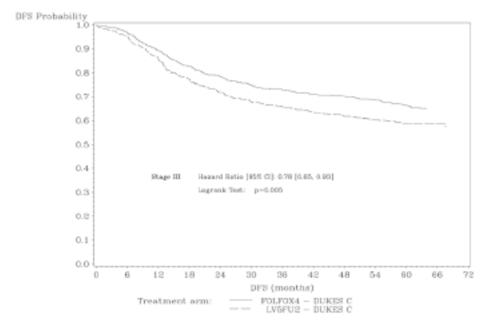


Figure 3 - DFS Kaplan-Meier curves by treatment arm in Stage III patients (cutoff: 1 June 2006) – ITT population

The following table summarizes the overall survival (OS) results in the overall randomized population and in patients with stage II and III disease, based on the ITT analysis.

Table 19 - Summary of OS analysis - ITT analysis

Parameter	Oxaliplatin + Infusional 5-FU/LV	Infusional 5-FU/LV
Overall		
N	1123	1123
Number of death events (%)	245 (21.8)	283 (25.2)
Hazard ratio* [95% CI]	0.84 [0.71, 1.00]	
Stage III (Dukes' C)		
N	672	675
Number of death events (%)	182 (27.1)	220 (32.6)
Hazard ratio* [95% CI]	0.80 [0.65, 0.97]	
Stage II (Dukes' B2)		
N	451	448
Number of death events (%)	63 (14.0)	63 (14.1)
Hazard ratio* [95% CI]	1.00 [0.70, 1.41]	

*A hazard ratio of less than 1.00 favors Oxaliplatin + Infusional 5-fluorouracil/leucovorin
Data cut off for overall survival 16 January 2007

14.2 Combination Therapy with Oxaliplatin for Injection and 5-fluorouracil/leucovorin in Patients Previously Untreated for Advanced Colorectal Cancer

A North American, multicenter, open-label, randomized controlled study was sponsored by the National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer Treatment Group (NCCTG). The study had 7 arms at different times during its conduct, four of which were closed due to either changes in the standard of care, toxicity, or simplification. During the study, the control arm was changed to irinotecan plus 5-fluorouracil/leucovorin. The results reported below compared the efficacy and safety of two experimental regimens, Oxaliplatin for Injection in combination with infusional 5-fluorouracil/leucovorin and a combination of Oxaliplatin for Injection plus irinotecan, to an approved control regimen of irinotecan plus 5-fluorouracil/leucovorin in 795 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. After completion of enrollment, the dose of irinotecan plus 5-fluorouracil/leucovorin was decreased due to toxicity. Patients had to be at least 18 years of age, have known locally advanced, locally recurrent, or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent, histologically proven colorectal adenocarcinoma, measurable or evaluable disease, with an ECOG performance status 0,1, or 2. Patients had to have granulocyte count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin ≥ 9.0 gm/dL, creatinine ≤ 1.5 x ULN, total bilirubin ≤ 1.5 mg/dL, AST ≤ 5 x ULN, and alkaline phosphatase ≤ 5 x ULN. Patients may have received adjuvant therapy for resected Stage II or III disease without recurrence within 12 months. The patients were stratified for ECOG performance status (0, 1 vs. 2), prior adjuvant chemotherapy (yes vs. no), prior immunotherapy (yes vs. no), and age (<65 vs. ≥ 65 years). Although no post study treatment was specified in the protocol, 65 to 72% of patients received additional post study chemotherapy after study treatment discontinuation on all arms. Fifty-eight percent of patients on the Oxaliplatin for Injection plus 5-fluorouracil/leucovorin arm received an irinotecan-containing regimen and 23% of patients on the irinotecan plus 5-fluorouracil/leucovorin arm received oxaliplatin-containing regimens. Oxaliplatin was not commercially available during the trial.

The following table presents the dosing regimens of the three arms of the study.

Table 20 – Dosing Regimens in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (FOLFOX4) (N=267)	Day 1: Oxaliplatin: 85 mg/m^2 (2-hour infusion) + LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
irinotecan + 5-FU/LV (IFL) (N=264)	Day 1: irinotecan 125 mg/m^2 as a 90–min infusion + LV 20 mg/m^2 as a 15-min infusion or intravenous push, followed by 5-FU 500 mg/m^2 intravenous bolus weekly x 4	every 6 weeks
Oxaliplatin + irinotecan (IROX) (N=264)	Day 1: Oxaliplatin: 85 mg/m^2 intravenous (2-hour infusion) + irinotecan 200 mg/m^2 intravenous over 30 minutes	every 3 weeks

The following table presents the demographics of the patient population entered into this study.

Table 21 – Patient Demographics in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

	Oxaliplatin + 5-FU/LV N=267	irinotecan + 5-FU/LV N=264	Oxaliplatin + irinotecan N=264
Sex: Male (%)	58.8	65.2	61.0
Female (%)	41.2	34.8	39.0
Median age (years)	61.0	61.0	61.0
<65 years of age (%)	61	62	63
≥65 years of age (%)	39	38	37
ECOG (%)			
0.1	94.4	95.5	94.7
2	5.6	4.5	5.3
Involved organs (%)			
Colon only	0.7	0.8	0.4
Liver only	39.3	44.3	39.0
Liver + other	41.2	38.6	40.9
Lung only	6.4	3.8	5.3
Other (including lymph nodes)	11.6	11.0	12.9
Not reported	0.7	1.5	1.5
Prior radiation (%)	3.0	1.5	3.0
Prior surgery (%)	74.5	79.2	81.8
Prior adjuvant (%)	15.7	14.8	15.2

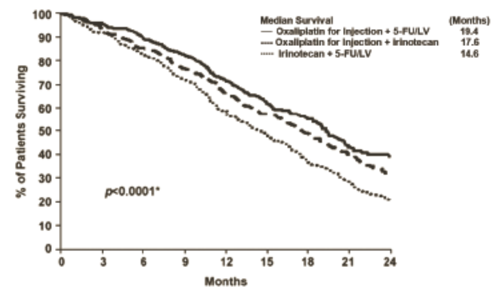
The length of a treatment cycle was 2 weeks for the Oxaliplatin for Injection and 5-fluorouracil/leucovorin regimen; 6 weeks for the irinotecan plus 5-fluorouracil/leucovorin regimen; and 3 weeks for the Oxaliplatin for Injection plus irinotecan regimen. The median number of cycles administered per patient was 10 (23.9 weeks) for the Oxaliplatin for Injection and 5-fluorouracil/leucovorin regimen, 4 (23.6 weeks) for the irinotecan plus 5-fluorouracil/leucovorin regimen, and 7 (21.0 weeks) for the Oxaliplatin for Injection plus irinotecan regimen. Patients treated with the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination had a significantly longer time to tumor progression based on investigator assessment, longer overall survival, and a significantly higher confirmed response rate based on investigator assessment compared to patients given irinotecan plus 5-fluorouracil/leucovorin. The following table summarizes the efficacy results.

Table 22 – Summary of Efficacy

	Oxaliplatin + 5-FU/LV N=267	irinotecan + 5-FU/LV N=264	Oxaliplatin + irinotecan N=264
Survival (ITT)			
Number of deaths N (%)	155 (58.1)	192 (72.7)	175 (66.3)
Median survival (months)	19.4	14.6	17.6
Hazard Ratio and (95% confidence interval)	0.65 (0.53-0.80)*		
P-value	<0.0001*	-	-
TTP (ITT, investigator assessment)			
Percentage of progressors	82.8	81.8	89.4
Median TTP (months)	8.7	6.9	6.5
Hazard Ratio and (95% confidence interval) ***	0.74 (0.61-0.89)*		
P-value	0.0014*	-	-
Response Rate (investigator assessment)**			
Patients with measurable disease	210	212	215
Complete response N (%)	13 (6.2)	5 (2.4)	7 (3.3)
Partial response N (%)	82 (39.0)	64 (30.2)	67 (31.2)
Complete and partial response N (%)	95 (45.2)	69 (32.5)	74 (34.4)
95% confidence interval	(38.5 – 52.0)	(26.2 – 38.9)	(28.1 – 40.8)
P-value	0.0080*	-	-

*Compared to irinotecan plus 5-fluorouracil/leucovorin (IFL) arm
**Based on all patients with measurable disease at baseline
The numbers in the response rate and TTP analysis are based on unblinded investigator assessment.
***A hazard ratio of less than 1.00 favors Oxaliplatin + Infusional 5-fluorouracil/leucovorin

Figure 4 illustrates the Kaplan-Meier survival curves for the comparison of Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination and Oxaliplatin for Injection plus irinotecan to irinotecan plus 5-fluorouracil/leucovorin.



* Log rank comparing Oxaliplatin plus 5-FU/LV to irinotecan plus 5-FU/LV.

Figure 4 – Kaplan-Meier Overall Survival by treatment arm

A descriptive subgroup analysis demonstrated that the improvement in survival for Oxaliplatin for Injection plus 5-fluorouracil/leucovorin compared to irinotecan plus 5-fluorouracil/leucovorin appeared to be maintained across age groups, prior adjuvant therapy, and number of organs involved. An estimated survival advantage in Oxaliplatin for Injection plus 5-fluorouracil/leucovorin versus irinotecan plus 5-fluorouracil/leucovorin was seen in both genders; however it was greater among women than men. Insufficient subgroup sizes prevented analysis by race.

14.3 Combination Therapy with Oxaliplatin for Injection and 5-fluorouracil/leucovorin in Previously Treated Patients with Advanced Colorectal Cancer

A multicenter, open-label, randomized, three-arm controlled study was conducted in the US and Canada comparing the efficacy and safety of Oxaliplatin for Injection in combination with an infusional schedule of 5-fluorouracil/leucovorin to the same dose and schedule of 5-fluorouracil/leucovorin alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or within 6 months of first-line therapy with bolus 5-fluorouracil/leucovorin and irinotecan. The study was intended to be analyzed for response rate after 450 patients were enrolled. Survival will be subsequently assessed in all patients enrolled in the completed study. Accrual to this study is complete, with 821 patients enrolled. Patients in the study had to be at least 18 years of age, have unresectable, measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky performance status > 50%. Patients had to have SGOT(AST) and SGPT(ALT) ≤ 2x the institution's upper limit of normal (ULN), unless liver metastases were present and documented at baseline by CT or MRI scan, in which case ≤ 5x ULN was permitted. Patients had to have alkaline phosphatase ≤ 2x the institution's ULN, unless liver metastases were present and documented at baseline by CT or MRI scan, in which cases ≤ 5x ULN was permitted. Prior radiotherapy was permitted if it had been completed at least 3 weeks before randomization. The dosing regimens of the three arms of the study are presented in the table below.

Table 23 – Dosing Regimens in Refractory and Relapsed Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (N =152)	Day 1: Oxaliplatin: 85 mg/m^2 (2-hour infusion) + LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
5-FU/LV (N=151)	Day 1: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
Oxaliplatin (N=156)	Day 1: Oxaliplatin 85 mg/m^2 (2-hour infusion)	every 2 weeks

Patients entered into the study for evaluation of response must have had at least one unidimensional lesion measuring ≥ 20 mm using conventional CT or MRI scans, or ≥ 10 mm using a spiral CT scan. Tumor response and progression were assessed every 3 cycles (6 weeks) using the Response Evaluation Criteria in Solid Tumors (RECIST) until radiological documentation of progression or for 13 months following the first dose of study drug(s), whichever came first. Confirmed responses were based on two tumor assessments separated by at least 4 weeks. The demographics of the patient population entered into this study are shown in the table below.

Table 24 – Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial

	5-FU/LV (N = 151)	Oxaliplatin (N = 156)	Oxaliplatin + 5-FU/LV (N = 152)
Sex: Male (%)	54.3	60.9	57.2
Female (%)	45.7	39.1	42.8
Median age (years)	60.0	61.0	59.0
Range	21-80	27-79	22-88
Race (%)			
Caucasian	87.4	84.6	88.8
Black	7.9	7.1	5.9
Asian	1.3	2.6	2.6
Other	3.3	5.8	2.6
KPS (%)			
70 – 100	94.7	92.3	95.4
50 – 60	2.6	4.5	2.0
Not reported	2.6	3.2	2.6
Prior radiotherapy (%)	25.2	19.2	25.0
Prior pelvic radiation (%)	18.5	13.5	21.1
Number of metastatic sites (%)			
1	27.2	31.4	25.7
≥2	72.2	67.9	74.3
Liver involvement (%)			
Liver only	22.5	25.6	18.4
Liver + other	60.3	59.0	53.3

The median number of cycles administered per patient was 6 for the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination and 3 each for 5-fluorouracil/leucovorin alone and Oxaliplatin for Injection alone.

Patients treated with the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin had an increased response rate compared to patients given 5-fluorouracil/leucovorin or oxaliplatin alone. The efficacy results are summarized in the tables below.

Table 25 - Response Rates (ITT Analysis)

Best Response	5-FU/LV (N=151)	Oxaliplatin (N=156)	Oxaliplatin + 5-FU/LV (N=152)
CR	0	0	0
PR	0	2 (1%)	13 (9%)
p-value	0.0002 for 5-FU/LV vs. Oxaliplatin + 5-FU/LV		
95%CI	0-2.4%	0.2-4.6%	4.6-14.2%

Table 26 - Summary of Radiographic Time to Progression*

Arm	5-FU/LV (N=151)	Oxaliplatin (N=156)	Oxaliplatin + 5-FU/LV (N=152)
No. of Progressors	74	101	50
No. of patients with no radiological evaluation beyond baseline	22 (15%)	16 (10%)	17 (11%)
Median TTP (months)	2.7	1.6	4.6
95% CI	1.8-3.0	1.4-2.7	4.2-6.1

*This is not an ITT analysis. Events were limited to radiographic disease progression documented by independent review of radiographs. Clinical progression was not included in this analysis, and 18% of patients were excluded from the analysis based on unavailability of the radiographs for independent review.

At the time of the interim analysis 49% of the radiographic progression events had occurred. In this interim analysis an estimated 2-month increase in median time to radiographic progression was observed compared to 5-fluorouracil/leucovorin alone.

Of the 13 patients who had tumor response to the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, 5 were female and 8 were male, and responders included patients <65 years old and ≥ 65 years old. The small number of non-Caucasian participants made efficacy analyses in these populations uninterpretable.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Oxaliplatin for Injection is supplied in clear, glass, single-use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient.

NDC 61703-361-35: 50 mg single use vial individually packaged in a carton.

NDC 61703-362-50: 100 mg single use vial individually packaged in a carton.

16.2 Storage

Store under normal lighting conditions at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°- 86°F) [see USP controlled room temperature]. Do not freeze.

16.3 Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from Oxaliplatin for Injection. The use of gloves is recommended. If a solution of Oxaliplatin for Injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If Oxaliplatin for Injection contacts the mucous membranes, flush thoroughly with water.

Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients and patients' caregivers should be informed of the expected side effects of Oxaliplatin for Injection, particularly its neurologic effects, both the acute, reversible effects and the persistent neurosensory toxicity. Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects. Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.

Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhea, or evidence of infection develop.

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties occur, or signs of allergic reaction appear.

No studies on the effects on the ability to drive and use machines have been performed. However oxaliplatin treatment resulting in an increase risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

Oxaliplatin for Injection

Read this information carefully before you start using Oxaliplatin for Injection. It will help you learn more about Oxaliplatin for Injection. This information does not take the place of talking to your doctor about your medical condition or your treatment. Ask your doctor about any questions you have.

What is the most important information I should know about Oxaliplatin for Injection?

Oxaliplatin for Injection can cause serious allergic reactions.

In people who get severe allergic reactions while taking platinum medicines, death can occur.

Get emergency help right away if you:

- **Suddenly have trouble breathing.**
- **Feel like your throat is closing up.**

Call your doctor right away if you have any signs of allergic reaction:

- Rash
- Flushed face
- Hives
- Itching
- Swelling of your lips or tongue
- Sudden cough
- Dizziness or feel faint
- Sweating
- Chest pain

If you have vision problems while taking Oxaliplatin for Injection

- Do not drive, operate heavy machines, or engage in dangerous activities.

See "What are the possible side effects of Oxaliplatin for Injection" for information on other serious side effects.

What is Oxaliplatin for Injection?

Oxaliplatin for Injection is an anticancer (chemotherapy) medicine that is used with other anti-cancer medicines called 5-fluorouracil and leucovorin to treat adults with:

- stage III colon cancer after surgery to remove the tumor
- advanced colon or rectal cancer (colo-rectal cancer).

Oxaliplatin for Injection with infusional 5-fluorouracil and leucovorin was shown to lower the chance of colon cancer returning when given to patients with stage III colon cancer after surgery to remove the tumor. Oxaliplatin for Injection also increases survival in patients with stage III colon cancer. Oxaliplatin for Injection with infusional 5-fluorouracil and leucovorin was also shown to increase survival, shrink tumors and delay growth of tumors in some patients with advanced colorectal cancer.

It is not known if Oxaliplatin for Injection works in children.

Who should not use Oxaliplatin for Injection?

Do not use Oxaliplatin for Injection if you are allergic to any of the ingredients in Oxaliplatin for Injection or other medicines that contain platinum. Cisplatin (Platinol®) and carboplatin (Paraplatin®) are other chemotherapy medicines that also contain platinum. See the end of this leaflet for a list of the ingredients in Oxaliplatin for Injection.

What should I tell my doctor before treatment with Oxaliplatin for Injection?

Tell your doctor about all your medical conditions including, if you are:

- Pregnant or planning to become pregnant. Oxaliplatin for Injection may harm your unborn child. You should avoid becoming pregnant while taking Oxaliplatin for Injection. Talk with your doctor about how to avoid pregnancy.
- Breast feeding or plan to breast feed. We do not know if Oxaliplatin for Injection can pass through your milk and if it can harm your baby. You will need to decide whether to stop breast feeding or not to take Oxaliplatin for Injection.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Oxaliplatin for Injection may affect how other medicines work in your body.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How is Oxaliplatin for Injection given to me?

Oxaliplatin for Injection is given to you through your veins (blood vessels).

- Your doctor will prescribe Oxaliplatin for Injection in an amount that is right for you.
- Your doctor will treat you with several medicines for your cancer.
- It is very important that you do exactly what your doctor and nurse have taught you to do.
- Some medicines may be given to you before Oxaliplatin for Injection to help prevent nausea and vomiting.
- Oxaliplatin for Injection is given with 2 other chemotherapy medicines, leucovorin and 5-fluorouracil.
- Each treatment course is given to you over 2 days. You will receive Oxaliplatin for Injection on the first day only.
- There are usually 14 days between each chemotherapy treatment course.

Treatment Day 1:

Oxaliplatin for Injection and leucovorin are given through a thin plastic tube put into a vein (intravenous infusion or I.V.) and given for 2 hours. You will be watched by a healthcare provider during this time.

Right after the Oxaliplatin for Injection and leucovorin are finished, 2 doses of 5-fluorouracil will be given. The first dose is given right away into your I.V. tube. The second dose will be given into your I.V. tube over the next 22 hours, using a pump device.

Treatment Day 2:

You will not get Oxaliplatin for Injection on Day 2. Leucovorin and 5-fluorouracil will be given the same way as on Day 1.

During your treatment with Oxaliplatin for Injection:

- It is important for you to keep all appointments. Call your doctor if you must miss an appointment. There may be special instructions for you.
- Your doctor may change how often you get Oxaliplatin for Injection, how much you get, or how long the infusion will take.
- You and your doctor will discuss how many times you will get Oxaliplatin for Injection.

The 5-fluorouracil will be given through your I.V. with a pump. If you have any problems with the pump or the tube, call your doctor, your nurse, or the person who is responsible for your pump. Do not let anyone other than a healthcare provider touch your infusion pump or tubing.

What activities should I avoid while on treatment with Oxaliplatin for Injection?

- Avoid cold temperatures and cold objects. Cover your skin if you must go outside in cold temperatures.
- Do not drink cold drinks or use ice cubes in drinks.
- Do not put ice or ice packs on your body.

See the end of this leaflet, ("How can I reduce the side effects caused by cold temperatures?") for more information.

Talk with your doctor and nurse about your level of activity during treatment with Oxaliplatin for Injection. Follow their instructions.

What are the possible side effects of Oxaliplatin for Injection?

Oxaliplatin for Injection can cause serious side effects:

- **Serious allergic reactions.** See "What is the most important information I should know about Oxaliplatin for Injection?"
- **Nerve problems (peripheral neuropathy).** Oxaliplatin for Injection can affect how your nerves work and make you feel. Tell your doctor right away if you get any signs of nerve problems listed below:
  - Very sensitive to cold temperatures and cold objects
  - Trouble breathing, swallowing, or saying words, jaw tightness, odd feelings in your tongue, or chest pressure
  - Pain, tingling, burning (pins and needles, numb feeling) in your hands, feet, or around your mouth or throat, which may cause problems walking or performing activities of daily living.

The first signs of nerve problems may happen with the first treatment. The nerve problems can also start up to 2 days after treatment. If you develop nerve problems, the amount of Oxaliplatin for Injection in your next treatment may be changed or Oxaliplatin for Injection treatment may be stopped.

For information on ways to lessen or help with the nerve problems, see the end of this leaflet, "How can I reduce the side effects caused by cold temperatures?"

- **Lung problems** (interstitial fibrosis). Tell your doctor if you get a dry cough and have trouble breathing (shortness of breath) before your next treatment. These may be signs of a serious lung disease.
- **Liver problems** (hepatotoxicity). Your doctor will do blood tests to watch for this.
- **Harm to an unborn baby. Oxaliplatin for Injection may cause harm to your unborn baby.** See "What should I tell my doctor before treatment with Oxaliplatin for Injection?"

Common side effects with Oxaliplatin for Injection include:

- Decreased blood counts: Oxaliplatin for Injection can cause a decrease in neutrophils (a type of white blood cells important in fighting in bacterial infections), red blood cells (blood cells that carry oxygen to the tissues), and platelets (important for clotting and to control bleeding).

Call your doctor right away if you get any of the following signs of infection:

- Fever (temperature of 100.5 F or greater)
- Chills or shivering
- Cough that brings up mucus
- Burning or pain on urination
- Pain on swallowing
- Sore throat
- Redness or swelling at intravenous site
- Tell your doctor about any bleeding or bruising
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Mouth sores
- Stomach pain
- Decreased appetite
- Tiredness
- Eyesight (visual) problems including reversible short-term loss of vision. Tell your doctor about any eyesight changes.
- Injection site reactions. Reactions may include redness, swelling, pain, tissue damage
- Hair loss (alopecia)

Call your doctor if you get any of the following:

- Vomiting that does not go away
- Frequent, loose, watery bowel movements (Diarrhea)
- Signs of dehydration (too much water loss)
  - Tiredness
  - Thirst
  - Dry Mouth
  - Lightheadedness (dizziness)
  - Decreased urination

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Oxaliplatin for Injection. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How can I reduce the side effects caused by cold temperatures?

- Cover yourself with a blanket while you are getting your Oxaliplatin for Injection infusion.
- Do not breathe deeply when exposed to cold air.
- Wear warm clothing in cold weather at all times. Cover your mouth and nose with a scarf or a pull-down cap (ski cap) to warm the air that goes to your lungs.
- Wear gloves when taking things from the freezer or refrigerator.
- Drink fluids warm or at room temperature.
- Always drink through a straw.
- **Do not** use ice chips if you have nausea or mouth sores. Ask your nurse about what you can use.
- Be aware that most metals are cold to touch, especially in the winter. These include your car door and mailbox. Wear gloves to touch cold objects.
- Do not run the air-conditioning at high levels in the house or in the car in hot weather.
- If your body gets cold, warm-up the affected part. If your hands get cold, wash them with warm water.
- Always let your nurse and doctor know **before** your next treatment how well you did since your last visit.

This list is not complete and your healthcare provider may have other useful tips for helping you with these side effects.

General information about the safe and effective use of Oxaliplatin for Injection

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

This leaflet summarizes the most important information about Oxaliplatin for Injection. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Oxaliplatin for Injection that is written for health professionals.

What are the ingredients in Oxaliplatin for Injection?

Active ingredient: oxaliplatin

Inactive ingredient: lactose monohydrate

Manufactured by:
Hospira, Inc.
Lake Forest, Illinois
Product of Australia
Revision April 2009

Hospira

431485

Designer/Artworker (b) (6)
Date: 08/04/09
Version: 4

(b) (4)

Colour/s		Artwork Version	4
Black C	(b) (4)	Date of Preparation	22/10/08
		Artworker/Designer	(b) (6)

50 mg Single Use Vial NDC 61703-361-35

Sterile

Oxaliplatin for Injection

50 mg R_x only

(lyophilized)

For Intravenous Use Only

Must be reconstituted and diluted before use

Do not reconstitute with sodium chloride/chloride-containing solutions

Caution: Cytotoxic Agent

Each vial contains: 50 mg oxaliplatin. Inactive: 450 mg lactose monohydrate, NF.

Preservative free. Discard unused solution.

Usual Dosage: See package insert for complete product information.

Prior to Reconstitution: Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

See package insert for storage of reconstituted and diluted solutions.

Hospira, Inc.
Lake Forest, IL 60045
Product of Australia
484221

(01)00361703361356

(b) (4)

Colour/s		Artwork Version	3
Black C	(b) (4)	Date of Preparation	23/10/08
		Artworker/Designer	(b) (6)

100 mg Single Use Vial NDC 61703-362-50

Sterile

Oxaliplatin for Injection

100 mg

(lyophilized)

℞ only

For Intravenous Use Only
Must be reconstituted and diluted before use
Do not reconstitute with sodium chloride/chloride-containing solutions
Caution: Cytotoxic Agent

Each vial contains: 100 mg oxaliplatin. Inactive: 900 mg lactose monohydrate, NF.

Preservative free. Discard unused solution.

Usual Dosage: See package insert for complete product information.

Prior to Reconstitution: Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

See package insert for storage of reconstituted and diluted solutions.

Hospira, Inc.
Lake Forest, IL 60045
Product of Australia

484224

(01)00361703882566

(b) (4)

Colour/s			
Black C		Artwork Version	5
(b) (4)		Date of Preparation	24/10/08
All text & graphics will have UV Varnish		Artworker/Designer	(b) (6)

(01)00361703361356

484220

VIAL Hospira

Each vial contains:
50 mg oxaliplatin.
Inactive: 450 mg lactose monohydrate, NF.

Preservative free.
Discard unused solution.

Usual Dosage: See package insert for complete product information.

Prior to Reconstitution: Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Reconstitute with 10 mL of Water for Injection, USP or 5% Dextrose Injection, USP.

See package insert for storage of reconstituted and diluted solutions.

Store Upright.

Caution: Cytotoxic Agent

VIAL Hospira

1 x 50 mg Vial NDC 61703-361-35

Sterile

Oxaliplatin for Injection

50 mg

(lyophilized)

℞ only

For Intravenous Use Only
Must be reconstituted and diluted before use
Do not reconstitute with sodium chloride/chloride-containing solutions
Single Use Vial

Caution: Cytotoxic Agent

VIAL Hospira

Hospira, Inc.
Lake Forest, IL 60045
Product of Australia

Oxaliplatin for Injection 50 mg (lyophilized)

Sterile

VIAL Hospira

Oxaliplatin for Injection 50 mg (lyophilized)

(b) (4)

Colour/s		
Black C	Artwork Version	3
(b) (4)	Date of Preparation	23/10/08
All text & graphics will have UV Varnish	Artworker/Designer	(b) (6)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-815 Date of Submission: 09 FEB 2007 (Original)
Applicant's Name: Mayne Pharma
Established Name: Oxaliplatin for Injection 50 mg and 100 mg per vial- PF-SDV, Lyophilized
---

Labeling Deficiencies: Firm submitted e-draft.

1. CONTAINER

a. We encourage you to add “cytotoxic agent” to your labels.

b. List the in actives under an "inactive" category.

c. We are aware that the innovator uses tall man lettering as part of the established name. However, upon further review this product should not display tall man lettering. We acknowledge you have revised without regard for tall man lettering and have displayed "Oxaliplatin" rather than "OXALIplatin" and we find that acceptable.

2. CARTON -See comments under CONTAINER.

3. INSERT - Minor correction in the Highlighted section, second paragraph - revise "….. powder for solution for intravenous…".

4. PATIENT INFORMATION SHEET - Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed or draft electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION

ANDA Number	78-815
Date of Submission	
Applicant	Mayne Pharma
Drug Name	Oxaliplatin for Injection
Strength(s)	50 mg and 100 mg vials- PF- SDV lyophilized

LABELS AND LABELING

Container Labels
50 mg
100 mg
Carton labeling
50 mg
100 mg

Insert Labeling
Patient Information Draft

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of Eloxatin (Sanofi).

Reference Listed Drug

RLD on the 356(h) form	Eloxatin
NDA Number	21-492 (for Injection- Dc'ed) related NDA is 21-759 RTU solution
RLD established name	OXALIplatin Injection 50 MG AND 100 MG - PF-SDV
Firm	Sanofi Aventis US
Currently approved PI	SE8-008
AP Date	10 JAN 2007

RLD has (b) (4) supplement in (b) (4).

4. Patent Data For NDA 21-492

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5290961	12 JAN 2013 PEDS- 12 Jul 2013			PIV	Same As
5338874	07 APR 2013 PED- 07 Oct 2013			PIV	Same As
5420319	09 AUG 2016 PED- 09 Feb 2017			PIV	Same As
5716988	07 AUG 2015 PED- 07 Feb 2016		Only listed for 21-759	PIV	Same As

Exclusivity Data For NDA: 21-492

Code/sup	Expiration	Use Code	Description		Labeling Impact
NCE	09 AUG 2007 peds 09 Feb 2008				Same As

I-441	04 Nov 2007 peds 04 May 2008		USE COMBINATION WITH INFUSIONAL 5-FU/LV FOR ADJUVANT TREATMENT STAGE III COLON CANCER PTS WHO HAVE UNDERGONE COMPLETE RESECTION PRIMARY TUMOR-BASED ON IMPROVEMENT IN DISEASE FREE SURVIVAL, NO DEMONSTRATED BENEFIT OVERALL SURVIVAL AFTER 4YRS		Same As
M-61	10 JAN 2010 peds 10 JUL 2010		REVISIONS TO LABELING BASED ON DATA SUBMITTED IN RESPONSE TO PEDIATRIC WRITTEN REQUEST		Same As
I-425	09 JAN 2007 peds July 2007		ELOXATIN IN COMBINATION WITH INFUSIONAL 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR THE TREATMENT OF PATIENTS PREVIOUSLY UNTREATED FOR ADVANCED COLORECTAL CANCE		Same As

5. Storage Conditions:
   NDA – lyophilized for injection was discontinued for non safety and efficacy reasons. The Injection should be stored 25C(77F) excursions permitted to 15-30. Do not Freeze. Protect from light (keep in outer carton) discard Unused portion and (see package insert for storage of further diluted solutions). Also label must NOT consider Tall Man letter but must add instructions to do not mix or add to sodium chloride/chloride-containing solutions. Open vial is ok for 6 hours and infusion diluted solutions should be discarded 6 hours at RT and 24 hrs under refrigeration after preparation.
   ANDA – Oxaliplatin injection label is the same.
   USP – Not a USP item.
6. Dispensing Recommendations:
   NDA – Does not have on the label “Caution: Cytotoxic agent”
   ANDA – will add to label “Caution: Cytotoxic agent”
   USP - Preserve in Containers for sterile solids as described under Injections (1), Caution – Great care should be taken in handling carboplatin because it is a suspected carcinogen.7
7. Scoring: not applicable
8. Product Line:
   The innovator markets their product as a lyophilized powder to be reconstituted and Injections (50 mg , 100 mg, and 200 mg vials) 5 mg/mL PF single-dose. The applicant proposes to market only the 50 mg and 100 mg products powder.
9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Not applicable
10. Inactive Ingredients: lactose monhydrate.
11. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page **.**
12. Manufactured by Mayne Pharma in Australlia for Mayne in US.

Date of Review: 3/13/08 **Date of Submission: 09 FEB 2007**

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cc: ANDA: 78-815
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
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/s/

Angela Payne
3/13/2008 09:49:20 PM
LABELING REVIEWER

John Grace
3/16/2008 04:59:58 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-815 Date of Submission: 03 NOV 2008 and 19 NOV 2008

Applicant's Name: Mayne Pharma

Established Name: Oxaliplatin for Injection 50 mg and 100 mg per vial- PF-SDV, Lyophilized

---

Labeling Deficiencies:

1. **CONTAINER -** Satisfactory.
2. **CARTON** - Satisfactory.
3. **INSERT -** Please increase the resolution of the text to improve upon the tables and graphs as expressed in my recent telephone communication with you. Please resubmit.
4. **PATIENT INFORMATION SHEET -** Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed or draft electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD #2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION

ANDA Number	78-815
Date of Submission	
Applicant	Mayne Pharma
Drug Name	Oxaliplatin for Injection
Strength(s)	50 mg and 100 mg vials- PF- SDV lyophilized

LABELS AND LABELING SUMMARY

Container	Satisfactory in FPL Nov. 19, 2008
50 mg	\\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\container.pdf
100 mg	
Carton	Satisfactory in FPL Nov. 19, 2008
50 mg	\\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\carton.pdf
100 mg	
Insert	RESUBMIT
Patient Information	

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of Eloxatin (Sanofi).

Reference Listed Drug	
RLD on the 356(h) form	Eloxatin
NDA Number	21-492 (for Injection- Dc'ed) related NDA is 21-759 RTU solution
RLD established name	OXALIplatin Injection 50 MG AND 100 MG - PF-SDV
Firm	Sanofi Aventis US
Currently approved PI	SE8-010
AP Date	21 MAY 2008

RLD has (b) (4) opened supplements.

4. Patent Data For NDA 21-492

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5290961	12 JAN 2013 PEDS- 12 Jul 2013			PIV	Same As
5338874	07 APR 2013 PED- 07 Oct 2013			PIV	Same As
5420319	09 AUG 2016 PED- 09 Feb 2017			PIV	Same As
5716988	07 AUG 2015 PED- 07 Feb 2016		Only listed for 21-759	PIV	Same As

Exclusivity Data For NDA: 21-492

Code/sup	Expiration	Use Code	Description		Labeling Impact
NCE	09 AUG 2007 peds 09 Feb 2008				Same As

I-441	04 Nov 2007 peds 04 May 2008		USE COMBINATION WITH INFUSIONAL 5-FU/LV FOR ADJUVANT TREATMENT STAGE III COLON CANCER PTS WHO HAVE UNDERGONE COMPLETE RESECTION PRIMARY TUMOR-BASED ON IMPROVEMENT IN DISEASE FREE SURVIVAL, NO DEMONSTRATED BENEFIT OVERALL SURVIVAL AFTER 4YRS		Same As
M-61	10 JAN 2010 peds 10 JUL 2010		REVISIONS TO LABELING BASED ON DATA SUBMITTED IN RESPONSE TO PEDIATRIC WRITTEN REQUEST		Same As
I-425	09 JAN 2007 peds July 2007		ELOXATIN IN COMBINATION WITH INFUSIONAL 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR THE TREATMENT OF PATIENTS PREVIOUSLY UNTREATED FOR ADVANCED COLORECTAL CANCE		Same As

5. Storage Conditions:
   NDA – lyophilized for injection was discontinued for non safety and efficacy reasons. The Injection should be stored 25C(77F) excursions permitted to 15-30. Do not Freeze. Protect from light (keep in outer carton) discard Unused portion and (see package insert for storage of further diluted solutions). Also label must NOT consider Tall Man letter but must add instructions to do not mix or add to sodium chloride/chloride-containing solutions. Open vial is ok for 6 hours and infusion diluted solutions should be discarded 6 hours at RT and 24 hrs under refrigeration after preparation.
   ANDA – Oxaliplatin injection label is the same.
   USP – Not a USP item.
6. Dispensing Recommendations:
   NDA – Does not have on the label “Caution: Cytotoxic agent”
   ANDA – will add to label “Caution: Cytotoxic agent”
   USP - Preserve in Containers for sterile solids as described under Injections (1), Caution – Great care should be taken in handling carboplatin because it is a suspected carcinogen.7
7. Scoring: not applicable
8. Product Line:
   The innovator markets their product as a lyophilized powder to be reconstituted and Injections (50 mg , 100 mg, and 200 mg vials) 5 mg/mL PF single-dose. The applicant proposes to market only the 50 mg and 100 mg products powder.
9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Not applicable
10. Inactive Ingredients: lactose monhydrate.
11. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page **.**
12. Manufactured by Mayne Pharma in Australlia for Mayne in US.

Date of Review: 2/04/09 **Date of Submission: 11/19/08 and 11/03/08**

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cc: ANDA: 78-815
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/s/

Angela Payne
2/4/2009 11:09:47 AM
LABELING REVIEWER

John Grace
2/6/2009 12:23:17 PM
LABELING REVIEWER

APPROVAL SUMMARY #2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION

ANDA Number	78-815
Date of Submission	03 FEB 2009
Applicant	Mayne Pharma
Drug Name	Oxaliplatin for Injection
Strength(s)	50 mg and 100 mg vials- PF- SDV lyophilized

LABELS AND LABELING SUMMARY

Container 50 mg 100 mg	Satisfactory in FPL Nov. 19, 2008 \\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\container.pdf
Carton 50 mg 100 mg	Satisfactory in FPL Nov. 19, 2008 \\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\carton.pdf
Insert & Patient leaf	Satisfactory in FPL on Feb 3, 2009 \\Fdswa150\nonectd\N78815\N_000\2009-02-03\m1\us\114-labeling\pi.pdf Attached

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of Eloxatin (Sanofi).

Reference Listed Drug

RLD on the 356(h) form	Eloxatin
NDA Number	21-492 (for Injection- Dc'ed) related NDA is 21-759 RTU solution
RLD established name	OXALIplatin Injection 50 MG AND 100 MG - PF-SDV
Firm	Sanofi Aventis US
Currently approved PI	SE8-010
AP Date	21 MAY 2008

RLD has (b) (4) opened supplements. Do not use tall man lettering.

4. Patent Data For NDA 21-492

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5290961	12 JAN 2013 PEDS- 12 Jul 2013			PIV	Same As
5338874	07 APR 2013 PED- 07 Oct 2013			PIV	Same As
5420319	09 AUG 2016 PED- 09 Feb 2017			PIV	Same As
5716988	07 AUG 2015 PED- 07 Feb 2016		Only listed for 21-759	PIV	Same As

Exclusivity Data For NDA: 21-492

Code/sup	Expiration	Use Code	Description		Labeling Impact
NCE	09 AUG 2007 peds 09 Feb 2008				Same As

I-441	04 Nov 2007 peds 04 May 2008		USE COMBINATION WITH INFUSIONAL 5-FU/LV FOR ADJUVANT TREATMENT STAGE III COLON CANCER PTS WHO HAVE UNDERGONE COMPLETE RESECTION PRIMARY TUMOR-BASED ON IMPROVEMENT IN DISEASE FREE SURVIVAL, NO DEMONSTRATED BENEFIT OVERALL SURVIVAL AFTER 4YRS		Same As
M-61	10 JAN 2010 peds 10 JUL 2010		REVISIONS TO LABELING BASED ON DATA SUBMITTED IN RESPONSE TO PEDIATRIC WRITTEN REQUEST		Same As
I-425	09 JAN 2007 peds July 2007		ELOXATIN IN COMBINATION WITH INFUSIONAL 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR THE TREATMENT OF PATIENTS PREVIOUSLY UNTREATED FOR ADVANCED COLORECTAL CANCE		Same As

5. Storage Conditions:
   NDA – lyophilized for injection was discontinued for non safety and efficacy reasons. The Injection should be stored 25C(77F) excursions permitted to 15-30. Do not Freeze. Protect from light (keep in outer carton) discard Unused portion and (see package insert for storage of further diluted solutions). Also label must NOT consider Tall Man letter but must add instructions to do not mix or add to sodium chloride/chloride-containing solutions. Open vial is ok for 6 hours and infusion diluted solutions should be discarded 6 hours at RT and 24 hrs under refrigeration after preparation.
   ANDA – Oxaliplatin injection label is the same.
   USP – Not a USP item.
6. Dispensing Recommendations:
   NDA – Does not have on the label “Caution: Cytotoxic agent”
   ANDA – will add to label “Caution: Cytotoxic agent”
   USP - Preserve in Containers for sterile solids as described under Injections (1), Caution – Great care should be taken in handling carboplatin because it is a suspected carcinogen.7
7. Scoring: not applicable
8. Product Line:
   The innovator markets their product as a lyophilized powder to be reconstituted and Injections (50 mg , 100 mg, and 200 mg vials) 5 mg/mL PF single-dose. The applicant proposes to market only the 50 mg and 100 mg products powder.
9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Not applicable
10. Inactive Ingredients: lactose monhydrate.
11. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page **.**
12. Manufactured by Mayne Pharma in Australlia for Mayne in US.

Date of Review: 2/12/09 **Date of Submission: 03 FEB 2009**

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cc: ANDA: 78-815
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/s/

Angela Payne
2/12/2009 01:10:54 PM
LABELING REVIEWER

John Grace
2/17/2009 10:28:48 AM
LABELING REVIEWER

APPROVAL SUMMARY #3
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION

ANDA Number	78-815
Date of Submission	29 APR 2009
Applicant	Mayne Pharma
Drug Name	Oxaliplatin for Injection
Strength(s)	50 mg and 100 mg vials- PF- SDV lyophilized

LABELS AND LABELING SUMMARY

Container 50 mg 100 mg	Satisfactory in FPL Nov. 19, 2008 \\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\container.pdf
Carton 50 mg 100 mg	Satisfactory in FPL Nov. 19, 2008 \\Fdswa150\nonectd\N78815\N_000\2008-11-19\m1\us\114-labeling\carton.pdf
Insert & Patient leaf	Satisfactory in FPL on April 29, 2009 \\Fdswa150\nonectd\N78815\N_000\2009-04-29\m1\us\1-14-labeling\pi.pdf Attached

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of Eloxatin (Sanofi).

Reference Listed Drug

RLD on the 356(h) form	Eloxatin
NDA Number	21-492 (for Injection- Dc'ed) related NDA is 21-759 RTU solution
RLD established name	OXALIplatin Injection 50 MG AND 100 MG - PF-SDV
Firm	Sanofi Aventis US
Currently approved PI	SL-011
AP Date	13 MAR 2009

RLD has (b) (4) opened supplements. Do not use tall man lettering. The generic ANDAs do not share a common insert.

4. Patent Data For NDA 21-492

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5290961	12 JAN 2013 PEDS- 12 Jul 2013			PIV	Same As
5338874	07 APR 2013 PED- 07 Oct 2013			PIV	Same As
5420319	09 AUG 2016 PED- 09 Feb 2017			PIV	Same As
5716988	07 AUG 2015 PED- 07 Feb 2016		Only listed for 21-759	PIV	Same As

Exclusivity Data For NDA: 21-492

Code/sup	Expiration	Use Code	Description		Labeling Impact
NCE	09 AUG 2007 peds 09 Feb 2008				Same As

I-441	04 Nov 2007 peds 04 May 2008		USE COMBINATION WITH INFUSIONAL 5-FU/LV FOR ADJUVANT TREATMENT STAGE III COLON CANCER PTS WHO HAVE UNDERGONE COMPLETE RESECTION PRIMARY TUMOR-BASED ON IMPROVEMENT IN DISEASE FREE SURVIVAL, NO DEMONSTRATED BENEFIT OVERALL SURVIVAL AFTER 4YRS		Same As
M-61	10 JAN 2010 peds 10 JUL 2010		REVISIONS TO LABELING BASED ON DATA SUBMITTED IN RESPONSE TO PEDIATRIC WRITTEN REQUEST		Same As
I-425	09 JAN 2007 peds July 2007		ELOXATIN IN COMBINATION WITH INFUSIONAL 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR THE TREATMENT OF PATIENTS PREVIOUSLY UNTREATED FOR ADVANCED COLORECTAL CANCE		Same As

5. Storage Conditions:
   NDA – lyophilized for injection was discontinued for non safety and efficacy reasons. The Injection should be stored 25C(77F) excursions permitted to 15-30. Do not Freeze. Protect from light (keep in outer carton) discard Unused portion and (see package insert for storage of further diluted solutions). Also label must NOT consider Tall Man letter but must add instructions to do not mix or add to sodium chloride/chloride-containing solutions. Open vial is ok for 6 hours and infusion diluted solutions should be discarded 6 hours at RT and 24 hrs under refrigeration after preparation.
   ANDA – Oxaliplatin injection label is the same.
   USP – Not a USP item.
6. Dispensing Recommendations:
   NDA – Does not have on the label “Caution: Cytotoxic agent”
   ANDA – will add to label “Caution: Cytotoxic agent”
   USP - Preserve in Containers for sterile solids as described under Injections (1), Caution – Great care should be taken in handling carboplatin because it is a suspected carcinogen.7
7. Scoring: not applicable
8. Product Line:
   The innovator markets their product as a lyophilized powder to be reconstituted and Injections (50 mg , 100 mg, and 200 mg vials) 5 mg/mL PF single-dose. The applicant proposes to market only the 50 mg and 100 mg products powder.
9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Not applicable
10. Inactive Ingredients: lactose monhydrate.
11. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page **.**
12. Manufactured by Mayne Pharma in Australlia for Mayne in US.

Date of Review: 5/6/09 **Date of Submission: 29 MAR 2009**

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cc: ANDA: 78-815
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/s/

Angela Payne
5/7/2009 07:36:36 AM
LABELING REVIEWER

John Grace
5/7/2009 12:22:38 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

CHEMISTRY REVIEWS

ANDA 78-815

Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

Mayne Pharma Limited

Bita Mirzai-Azarm

Division of Chemistry I

Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-815

2. REVIEW #: 1

3. REVIEW DATE: 08-AUG-2007

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS: None (1st review)

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	09-FEB-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Mayne Pharma Limited
Address:	551 Blackburn Road Mt. Waverly, Victoria AUSTRALIA
Representative:	Ron Filler 5108 Grimm Drive Alexandria, VA 22304
Telephone:	703-566-9181

Fax: 703-566-9182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Oxaliplatin for Injection

9. LEGAL BASIS FOR SUBMISSION:

Eloxatin® (oxaliplatin for injection) - Sanofi Aventis (NDA 21-492), **discontinued**

The reference listed drug, Eloxatin® Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial, approved under NDA 021492, manufactured by Sanofi Aventis US, has been discontinued. Therefore, Mayne Pharma Limited makes reference to docket number 2006P-0291 filed on July 25, 2006 to determine whether Eloxatin® Oxaliplatin Lyophilised Powder for Injection has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons. The Citizen's Petition is pending. The application is acceptable provided the FDA determines that the reference product was not withdrawn due to safety or efficacy reasons.

10. PHARMACOL. CATEGORY:

Indicated to treat adults with stage III colon cancer after surgery to remove the tumor or with other anti-cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV) to treat adults with advanced colon or rectal cancer (colorectal cancer).

11. DOSAGE FORM:

Lyophilized powder for injection

12. STRENGTH/POTENCY:

50 mg/vial and 100 mg/vial (5 mg/mL upon reconstitution)

13. ROUTE OF ADMINISTRATION:

Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

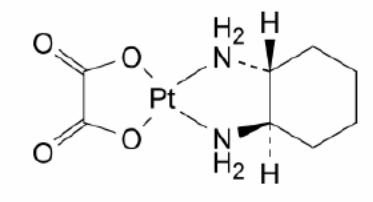
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature

- Oxaliplatin
  - (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-N,N']['ethanedioato(2)-O^1,O^2]platinum
- Oxalato(trans-l-1,2-diaminocyclohexane)platinum(II)
- [(R,R-1,2-Diaminocyclohexan)oxalatoplatin(II)]
- Oxaliplatinum

Structure



Molecular Formula

$C_8H_{14}N_2O_4Pt$

Molecular Weight

397.3

CAS Number
61825-94-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Inadequate	20-JUL-2007	Reviewed by K. Furnkranz
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Not necessary		
Labeling	Pending		
Bioequivalence	Acceptable	02-AUG-2007	Keri Suh
EA	21 CFR 25.31(a)	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-815

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – NA Minor
Labeling – Pending
Bio – Acceptable on 8/2/07
EER – Pending
Micro - Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment provided.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Oxaliplatin is a white or almost white crystalline powder, slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol with molecular formula of $C_8H_{14}N_2O_4Pt$ and molecular weight of 397.3. The DS manufacturer is (b) (4) (b) (4).

Drug Product:
Oxaliplatin for Injection is supplied as a lyophilized, sterile powder intended for intravenous administration following reconstitution with water for injection available in single-dose vials containing 50 mg or 100 mg of oxaliplatin. Each vial contains oxaliplatin and lactose monohydrate, NF.

B. Description of How the Drug Product is Intended to be Used

Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. (b) (4) Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

The Maximum Daily Dose is 147 mg (85 mg/m^2 x 1.73 m^2)
Surface area of average adult = 1.73 m^2

DS: IT = 0.10% QT = 0.15%
DP: IT = 0.2% QT = 0.2%

C. Basis for Approvability or Not-Approval Recommendation

Chemistry – NA Minor
Labeling – Pending
Bio – Acceptable on 8/2/07
EER – Pending
Micro - Pending

Following this page, 25 pages withheld in full (b)(4)

(b) (4)

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

R REGIONAL INFORMATION

R1 Executed Batch Records

Two batches of Oxaliplatin for Injection were manufactured in support of this application. All batches were manufactured at a scale which is greater than (b) (4)

R2 Comparability Protocols

There are no comparability protocols proposed for Oxaliplatin Injection.

R3 Methods Validation Package

Enclosed within the application.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Labeling review: Pending

Chemist's Review:

Description section

a. Structure: Satisfactory
b. Chemical names: Satisfactory
c. Molecular formulas: Satisfactory
d. Name of the inactive: Satisfactory

B. Environmental Assessment Or Claim Of Categorical Exclusion

21CFR 25.31 (a)

III. List Of Deficiencies To Be Communicated

See next page.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-815

APPLICANT: Mayne Pharma Limited

DRUG PRODUCT: Oxaliplatin Lyophilized Powder for Injection, 50 mg and 100 mg per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF (b) (4) s deficient and the DMF holder has been notified. Please ensure a response.

2. Please express the (b) (4) .

3. Please include (b) (4) .

4. Please include (b) (4)

5. We acknowledge that you use (b) (4)

6. As part of the in-process control, please include (b) (4)

7. Please include (b) (4) .

8. You have proposed (b) (4)

9. Please revise (b) (4) .

10. We acknowledge that you us (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your labeling and microbiological information are pending review. Deficiencies, if any will be communicated separately.

2. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

3. There appears to be a typographical error in reporting the [redacted] (b) (4) on Table 4.6.1 (p. 12 of 29). It should have been [redacted] (b) (4) instead of [redacted] (b) (4) Please confirm.

4. You have reported the Maximum Daily Dose (MDD) of the drug product as [redacted] (b) (4) Please note that MDD should have been reported as 147 mg (= 85 mg/m x 1.73 m).

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA: 78-815
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/8/13/07, 8/21/07 (revised)

HFD-625/M.Smela/

HFD-617/E.Chuh/

F/T by

V:\Chem Div I\Team 2\TL Folder\Draft\78815N01RBM.DOC

TYPE OF LETTER: NA MINOR

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

/s/

Bita Mirzai-Azarm
8/22/2007 02:42:40 PM
CHEMIST

Esther Chuh
8/22/2007 02:55:16 PM
CSO

Michael Smela
8/22/2007 03:51:22 PM
CHEMIST

ANDA 78-815

Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

Hospira Australia Pty Ltd.

Bita Mirzai-Azarm

Division of Chemistry I

Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-815

2. REVIEW #: 2

3. REVIEW DATE: 09-MAY-2008

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	09-FEB-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	26-NOV-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	**Hospira Australia Pty** Limited
Address:	551 Blackburn Road Mt. Waverly, Victoria AUSTRALIA
Representative:	Ron Filler 5108 Grimm Drive Alexandria, VA 22304
Telephone:	703-566-9181

Fax: 703-566-9182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Oxaliplatin for Injection

9. LEGAL BASIS FOR SUBMISSION:

Eloxatin® (oxaliplatin for injection) - Sanofi Aventis (NDA 21-492), **discontinued**

The reference listed drug, Eloxatin® Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial, approved under NDA 021492, manufactured by Sanofi Aventis US, has been discontinued. Therefore, Mayne Pharma Limited makes reference to docket number 2006P-0291 filed on July 25, 2006 to determine whether Eloxatin® Oxaliplatin Lyophilised Powder for Injection has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons. The application is acceptable provided the FDA determines that the reference product was not withdrawn due to safety or efficacy reasons.

10. PHARMACOL. CATEGORY:

Indicated to treat adults with stage III colon cancer after surgery to remove the tumor or with other anti-cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV) to treat adults with advanced colon or rectal cancer (colorectal cancer).

11. DOSAGE FORM:

Lyophilized powder for injection

12. STRENGTH/POTENCY:

50 mg/vial and 100 mg/vial (5 mg/mL upon reconstitution)

13. ROUTE OF ADMINISTRATION:

Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

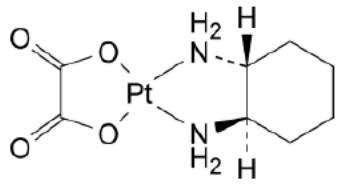
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature

- Oxaliplatin
  - (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-N,N']['ethanedioato(2)-O^1,O^2]platinum
- Oxalato(trans-l-1,2-diaminocyclohexane)platinum(II)
- [(R,R-1,2-Diaminocyclohexan)oxalatoplatin(II)]
- Oxaliplatinum

Structure



Molecular Formula

$C_8H_{14}N_2O_4Pt$

Molecular Weight

397.3

CAS Number
61825-94-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	03-DEC-2007	Reviewed by K. Furnkranz
	II			1	**Inadequate**	09-MAY-2008	Bita Mirzai-Azarm
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	**Pending**		
EES	Acceptable	02-OCT-2007	S. Adams
Methods Validation	Not necessary		
Labeling	**Deficient**	16-MAR-2008	Angela Payne
Bioequivalence	Acceptable	02-AUG-2007	Keri Suh
EA	21 CFR 25.31(a)	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-815

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – NA Minor
Labeling – Deficient on 3/16/08
Bio – Acceptable on 8/2/07
EER – Acceptable on 10/2/07
Micro - Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment provided.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Oxaliplatin is a white or almost white crystalline powder, slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol with molecular formula of $C_8H_{14}N_2O_4Pt$ and molecular weight of 397.3. The DS manufacturer is (b) (4) (b) (4). **As part of the 11/26/07 amendment an alternate manufacturing process for Oxaliplatin DS namely (b) (4) was added to the application. The manufacturer of the DS is still (b) (4) and the alternate process is under DMF (b) (4).**

Drug Product:

Oxaliplatin for Injection is supplied as a lyophilized, sterile powder intended for intravenous administration following reconstitution with water for injection available in single-dose vials containing 50 mg or 100 mg of oxaliplatin. Each vial contains oxaliplatin and lactose monohydrate, NF.

B. Description of How the Drug Product is Intended to be Used

Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. (b) (4) Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

The Maximum Daily Dose is 147 mg (85 mg/m^2 x 1.73 m^2)
Surface area of average adult = 1.73 m^2

DS: IT = 0.10% QT = 0.15%
DP: IT = 0.2% QT = 0.2%

C. Basis for Approvability or Not-Approval Recommendation

Chemistry – NA Minor
Labeling – Deficient on 3/16/08
Bio – Acceptable on 8/2/07
EER – Acceptable on 10/2/07
Micro - Pending

Following this page, 14 pages withheld in full (b)(4)

(b) (4)

[redacted]

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

R REGIONAL INFORMATION

R1 Executed Batch Records

Two batches of Oxaliplatin for Injection were manufactured in support of this amendment.

R2 Comparability Protocols

There are no comparability protocols proposed for Oxaliplatin Injection.

R3 Methods Validation Package

Enclosed within the application.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Labeling review: Deficient on 3/16/08 per Angela Payne.

B. Environmental Assessment Or Claim Of Categorical Exclusion

21CFR 25.31 (a)

III. List Of Deficiencies To Be Communicated

See next page.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-815

APPLICANT: Hospira Australia Pty Ltd.

DRUG PRODUCT: Oxaliplatin Lyophilized Powder for Injection, 50 mg and 100 mg per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF (b) (4) is deficient and the DMF holder has been notified. Please ensure a response.

2. Your proposed (b) (4) .

3. You proposed not tc (b) (4) .

4. The limit for the Uniformity of content test in the release specifications should be stated as "Complies with USP <905>".

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your labeling information has been reviewed and deficiencies have been communicated to you. Please respond to the deficiencies.

2. Your microbiological information is pending review. Deficiencies, if any, will be communicated separately.

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their

ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA: 78-815
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/5/14/08 (revised)

HFD-625/M.Smela/

HFD-617/E.Chuh/

F/T by

V:\Chem Div I\Team 2\TL Folder\Draft\78815N02RBM.DOC

TYPE OF LETTER: NA MINOR

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

/s/

Bita Mirzai-Azarm
5/16/2008 10:15:03 AM
CHEMIST

Esther Chuh
5/19/2008 12:02:54 PM
CSO

Michael Smela
5/20/2008 08:27:30 AM
CHEMIST

ANDA 78-815

Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

Hospira Worldwide, Inc.

Bita Mirzai-Azarm

Division of Chemistry I

Review #3

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-815

2. REVIEW #: 3

3. REVIEW DATE: 25-AUG-2008

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	09-FEB-2007
Major Amendment	26-NOV-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	01-AUG-2008
Telephone Amendment	29-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name: **Hospira Worldwide, Inc.**

Address: **275 North Field Drive**
Dept. 389, Bldg. H2-2N

Chemistry Review Data Sheet

Lake Forest, IL 60045-5046
Representative: **Laurie Wojtko**

Telephone: **224-212-6158**

Fax: **224-212-5401**

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Oxaliplatin for Injection

9. LEGAL BASIS FOR SUBMISSION:

Eloxatin® (oxaliplatin for injection) - Sanofi Aventis (NDA 21-492), **discontinued**

The reference listed drug, Eloxatin® Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial, approved under NDA 021492, manufactured by Sanofi Aventis US, has been discontinued. Therefore, Mayne Pharma Limited makes reference to docket number 2006P-0291 filed on July 25, 2006 to determine whether Eloxatin® Oxaliplatin Lyophilised Powder for Injection has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons. The application is acceptable provided the FDA determines that the reference product was not withdrawn due to safety or efficacy reasons.

10. PHARMACOL. CATEGORY:

Indicated to treat adults with stage III colon cancer after surgery to remove the tumor or with other anti-cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV) to treat adults with advanced colon or rectal cancer (colorectal cancer).

11. DOSAGE FORM:

Lyophilized powder for injection

12. STRENGTH/POTENCY:

50 mg/vial and 100 mg/vial (5 mg/mL upon reconstitution)

13. ROUTE OF ADMINISTRATION:

Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

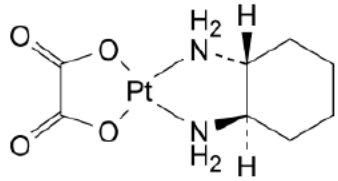
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature

- Oxaliplatin
  - (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-N,N']['ethanedioato(2)-O^1,O^2]platinum
- Oxalato(trans-l-1,2-diaminocyclohexane)platinum(II)
- [(R,R-1,2-Diaminocyclohexan)oxalatoplatin(II)]
- Oxaliplatinum

Structure



Molecular Formula

$C_8H_{14}N_2O_4Pt$

Molecular Weight

397.3

CAS Number
61825-94-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	07-JUL-2008	Reviewed by K. Furnkranz

Chemistry Review Data Sheet

20054	II	W.C. Heraeus GmbH	Oxaliplatin	3	**Adequate**	11-JUL-2008	Bita Mirzai-Azarm
(b) (4)	III	(b) (4)		4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	**Pending**		
EES	Acceptable	02-OCT-2007	S. Adams
Methods Validation	Not necessary		
Labeling	**Deficient**	16-MAR-2008	Angela Payne
Bioequivalence	Acceptable	02-AUG-2007	Keri Suh
EA	21 CFR 25.31(a)	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Minor Amendment

The Chemistry Review for ANDA 78-815

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – Acceptable
Labeling – Deficient on 3/16/08
Bio – Acceptable on 8/2/07
EER – Acceptable on 10/2/07
Micro - Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment provided.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Oxaliplatin is a white or almost white crystalline powder, slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol with molecular formula of $C_8H_{14}N_2O_4Pt$ and molecular weight of 397.3. The DS manufacturer is (b) (4) (b) (4) **As part of the 11/26/07 amendment an alternate manufacturing process for Oxaliplatin DS namely (b) (4) was added to the application. The manufacturer of the DS is still (b) (4) and the alternate process is under DMF (b) (4).**

Drug Product:
Oxaliplatin for Injection is supplied as a lyophilized, sterile powder intended for intravenous administration following reconstitution with water for injection available in single-dose vials containing 50 mg or 100 mg of oxaliplatin. Each vial contains oxaliplatin and lactose monohydrate, NF.

B. Description of How the Drug Product is Intended to be Used

Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. (b) (4) Oxaliplatin for Injection, used in combination with infusional 5 FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

The Maximum Daily Dose is 147 mg (85 mg/m^2 x 1.73 m^2)
Surface area of average adult = 1.73 m^2

DS: IT = 0.10% QT = 0.15%
DP: IT = 0.2% QT = 0.2%

C. Basis for Approvability or Not-Approval Recommendation

Chemistry – Acceptable
Labeling – Deficient on 3/16/08
Bio – Acceptable on 8/2/07
EER – Acceptable on 10/2/07
Micro - Pending

Following this page, 11 pages withheld in full (b)(4)

A APPENDICES
A.1 Facilities and Equipment (biotech only)
A.2 Adventitious Agents Safety Evaluation
A.3 Novel Excipients

R REGIONAL INFORMATION
R1 Executed Batch Records
Two batches of Oxaliplatin for Injection were manufactured in support of the previous amendment.

R2 Comparability Protocols
There are no comparability protocols proposed for Oxaliplatin Injection.

R3 Methods Validation Package
Enclosed within the application.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert
Labeling review: Deficient on 3/16/08 per Angela Payne.

B. Environmental Assessment Or Claim Of Categorical Exclusion
21CFR 25.31 (a)

III. List Of Deficiencies To Be Communicated
None

cc: ANDA: 78-815
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/8/29/08 (revised)

HFD-625/M.Smela/

HFD-617/E.Chuh/

F/T by

V:\Chem Div I\Team 2\TL Folder\Draft\78815N03RBM.DOC

TYPE OF LETTER: Chemistry Complete (labeling deficient, micro pending)

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

/s/

Bita Mirzai-Azarm
9/2/2008 12:05:14 PM
CHEMIST

The option to link to the August 29, 2008 telephone amendment was not available. I linked it to the August 1, 2008 minor amendment.

Michael Smela
9/2/2008 01:24:53 PM
CHEMIST

ANDA 78-815

Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

Hospira Worldwide, Inc.

Bita Mirzai-Azarm

Division of Chemistry I

Review #3 (Addendum)

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA: 78-815 (Addendum to CR #3)

APPLICANT: Hospira Worldwide, Inc.

DRUG PRODUCT: Oxaliplatin for Injection, 50 mg and 100 mg per vial

The following telephone amendment was covered as part of CR #3:

August 29, 2008 telephone amendment:

- The test for residual solvents has been added to the DP release specification. The acceptance criterion is "Complies with USP <467>".
- Vendor Declaration Statements are provided in 3.2.P.4.4 [redacted (b) (4)].

  NOTE: Hospira will no longer use [redacted (b) (4)] as a supplier of lactose. Only the [redacted (b) (4)] vendor statement for lactose is included.

Commitment is provided to reassess <467> if vendors are changed.

On September 4, 2008 the applicant submitted a Gratuitous Amendment – Compliance with USP <467> Residual Solvents. Information provided is no different from the August 29, 2008 telephone amendment.

For the record:

DMF [redacted (b) (4)]: Adequate
DMF [redacted]: Adequate
Labeling: Deficient in DFS
Micro: Pending

cc: ANDA: 78-815
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/9/19/08 (revised)

HFD-625/M.Smela/

HFD-617/E.Chuh/

F/T by

V:\Chem Div I\Team 2\TL Folder\Draft\78815addendumN03RBM.DOC

TYPE OF LETTER: Chemistry Complete (labeling deficient, micro pending)

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

/s/

Bita Mirzai-Azarm
9/19/2008 12:56:05 PM
CHEMIST

Michael Smela
9/19/2008 12:59:30 PM
CHEMIST
The ANDA may be AP when micro and labeling are acceptable provided DMFs (b) (4) remain adequate, no USP monographs publish and no new cmc amendments submitted

ANDA 78-815

Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

Hospira Worldwide, Inc.

Bita Mirzai-Azarm

Division of Chemistry I

Review #3 (Addendum - PF)

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA: 78-815 (Addendum to CR #3 regarding PF monograph)

APPLICANT: Hospira Worldwide, Inc.

DRUG PRODUCT: Oxaliplatin for Injection, 50 mg and 100 mg per vial

February 5, 2009 Telephone Amendment:
The applicant commits to update it's DS specs to comply with the official oxaliplatin monograph once it becomes effective in the USP.
Satisfactory

For the Records:

DMF (b) (4):	*Adequate on 7/7/08*
DMF :	*Adequate on 9/19/08*
Labeling:	*Acceptable on 2/17/09 by Angela Payne*
Micro:	*Satisfactory per Lisa Shelton on 2/2/09*

Chemistry Assessment Section

cc: ANDA: 78-815
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/2/11/09

HFD-625/K.Furnkranz/

HFD-617/E.Chuh/

V:\Chem Div I\Team 2\TL Folder\ANDA\78815N03addendum(PF)RBM.DOC

TYPE OF LETTER: ANDA APPROVAL

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/s/

Bita Mirzai-Azarm
2/26/2009 09:26:47 AM
CHEMIST

Esther Chuh
2/26/2009 02:24:17 PM
CHEMIST

Kenneth Furnkranz
3/4/2009 04:51:23 PM
CHEMIST

Final Approval Following a Tentative Approval
Abbreviated New Drug Application Regulatory Assessment

---

1. ANDA # 78-815

2. NAME AND ADDRESS OF APPLICANT
Hospira Worldwide PTY
Attention: Laurie Wojtko
Senior Associate, Global Regulatory Affairs
275 North Field Drive
D-0389, Bldg H2-2N
Lake Forest, IL 60045

3. LEGAL BASIS FOR SUBMISSION
Eloxatin® (Oxaliplatin for Injection)-Sanofi Aventis (NDA 21-492)

Patent Certification: P-IV

U.S. Patent Number	Expiration Date
5,290,961 (the '961 patent)	July 12, 2013
5,338,874 (the '874 patent)	October 7, 2013
5,420,319 (the '319 patent)	February 9, 2017

4. PROPRIETARY NAME
n/a

5. NONPROPRIETARY NAME
Oxaliplatin for Injection, (Preservative-Free), packaged in 50 mg and 100 mg Single-use Vials

6. CURRENT SUBMISSIONS AND OTHER DATES:

2/9/2007	Original
5/22/2009	ANDA Tentatively Approved
9/3/2009	Minor Amendment: Request for Final Approval

7. PHARMACOLOGICAL CATEGORY
Antineoplastic agent

8. Rx or OTC
Rx

9. SAMPLES AND RESULTS
N/A

10. LABELING STATUS
Acceptable by Angela Payne, 5/7/2009

11. BIOEQUIVALENCY STATUS
Acceptable by Keri Suh, 8/2/2007

12. MICROBIOLOGY STATUS
Acceptable by Lisa S. Shelton, 2/2/2009

13. ESTABLISHMENT INSPECTION
Acceptable by S. Adams 10/2/2007

14. CONCLUSIONS AND RECOMMENDATIONS
ANDA Approvable

PROJECT MANAGER:	DATE COMPLETED:
Esther Chuh, Pharm. D.	9/29/2009

cc: ANDA
Division File
Field Copy

Endorsements:

HFD-617 E. Chuh/Project Manager
HFD-620 B. Cai/ Team Leader

V:\Chemistry Division I\Team 2\TL Folder\Draft\ANDA\78815.RA for AP

ANDA Approval

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78815	ORIG-1	HOSPIRA WORLDWIDE INC	OXALIPLATIN
ANDA-78815	ORIG-1	HOSPIRA WORLDWIDE INC	OXALIPLATIN

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/s/

EUNJUNG E CHUH
09/30/2009

BING CAI
09/30/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-815
Drug Product Name	Oxaliplatin Lyophilized Powder for Injection
Strength	50 mg/vial and 100 mg/vial
Applicant Name	Mayne Pharma Limited
Address	Mt. Waverly, Victoria, Australia
Submission Date(s)	February 9, 2007
Amendment Date(s)	N/A
Reviewer	Keri Suh, Pharm.D.
First Generic	NO

I. Submission Summary

A. Drug Product Information

Test Product	Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial
Reference Product	Eloxatin® Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial
RLD Manufacturer	Sanofi Aventis US
NDA No.	021492
RLD Approval Date	August 9, 2002 (per Orange Book)
Indication	Indicated to treat adults with stage III colon cancer after surgery to remove the tumor or with other anti-cancer medicines called 5-flurouracil (5-FU) and leucovorin (LV) to treat adults with advanced colon or rectal cancer (colorectal cancer).

B. Formulation

Ingredients	Mayne's Oxaliplatin for Injection (50 mg/vial)	Sanofi's Eloxatin® (50 mg/vial)
Oxaliplatin	50 mg	50 mg
Lactose Monohydrate, NF	450 mg	450 mg

Ingredients	Mayne's Oxaliplatin for Injection (100 mg/vial)	Sanofi's Eloxatin® (100 mg/vial)
Oxaliplatin	100 mg	100 mg
Lactose Monohydrate, NF	900 mg	900 mg

The reference listed drug, Eloxatin® Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial, approved under NDA 021492, manufactured by Sanofi Aventis US, has been discontinued. Therefore, Mayne Pharma Limited makes reference to docket number 2006P-0291 filed on July 25, 2006 to determine whether Eloxatin® Oxaliplatin Lyophilised Powder for Injection has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons. The Citizen's Petition is pending. The application is acceptable provided the FDA determines that the reference product was not withdrawn due to safety or efficacy reasons.

Recommendations

The Division of Bioequivalence agrees that the information submitted by Mayne Pharma Limited demonstrates that its test product, Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial, fall under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver is granted, provided the FDA determines that the reference product was not withdrawn from the market due to safety and/or efficacy reasons.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-815 APPLICANT: Mayne Pharma Limited

DRUG PRODUCT: Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-815
BIOEQUIVALENCE – ACCEPTABLE
Submission date: February 9, 2007
Amendment Dates: Amendment Date(s): N/A

1. **WAIVER** (WAI)

Strengths:
50 mg/vial and 100 mg/vial
Outcome: AC

Outcome: AC- Acceptable

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/s/

Keri Suh
8/1/2007 07:21:31 AM
BIOPHARMACEUTICS

Lizzie Sanchez
8/1/2007 08:30:22 AM
BIOPHARMACEUTICS

Dale Conner
8/2/2007 04:42:54 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

October 16, 2008

ANDA: 78-815

Drug Product Name
Proprietary: N/A
Non-proprietary: Oxaliplatin for Injection
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
02/09/2007	02/09/2007	N/A	08/07/2008

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Mayne Pharma Limited
Address: 551 Blackburn Road, Mt. Waverly, Victoria, AUSTRALIA
U.S. Agent
Name: Drug Development Consultants, Inc.
Address: 5108 Grimm Drive, Alexandria, VA 22304
Representative: Ron Filler
Telephone: 703-566-9181

Name of Reviewer: Lisa S.G. Shelton

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:
Mayne Pharma Limited
1 Lexia Place
Mulgrave
Victoria 3170
Australia

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized power for injection, IV, 50 mg/vial and 100 mg/vial, packaged in a 30 mL single-use vial and 50 mL single-use vial, respectively

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Cytoxic

B. SUPPORTING/RELATED DOCUMENTS:
Microbiology Review #1 and #2 for ANDA 77-790 (77-790 and 77-790a1, 12/8/06 and 3/20/07, M. Stevens-Riley)
Microbiology Review #1 and #2 for ANDA 78-796 (78-796 and 78-796a1, 11/1/07 and 1/8/08, J. Wells)

C. REMARKS:

ANDAs 78-813 and 78-815 are similar and sections of this review where the review content is the same are noted. The same overall manufacturing process (b) (4), sterilization of container/closure components and equipment, and filling lines are used with the following exceptions:

- the drug formulations differ although the API is the same
- while both drugs are filled on Lines (b) (4) the 78-813 drug is (b) (4) filled on Line (b) (4)
- the 78-815 drug is lyophilized after (b) (4)
- the same manufacturing equipment is used to process the packaging components, but the container/closure systems are not the same

All references to page and volume number refer to the blue jacket copies and the OGD-assigned volume numbers (Modules 1-3 in volumes 1.1-1.7) rather than the applicant-assigned volume numbers that are in the Table of Contents (Module 1 in volume 1 of 1, Module 2 in volume 1 of 1, and Module 3 in volumes 1-6 of 6). Of note, there is no volume 6 of 6 among the OGD numbered jackets

(also not in COMIS). This reviewer sees no reason to clarify the situation since the volume is anticipated to include information not needed for sterility assurance.

filename: 78-815.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies – Floor plans missing as well as location of lyophilizer. Insufficient information regarding environmental monitoring, integrity testing, validation of stopper depyrogenation, equipment sterilization, lyophilizer sterilization, media fills, and exhibit batches.

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk associated with the microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Lisa S.G. Shelton, Ph.D.
Microbiology Team Leader/Brenda Pillari, Ph.D.

C. CC Block
cc: Field Copy

Following this page, 24 pages withheld in full (b)(4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 78-815 APPLICANT: Mayne Pharma Limited

DRUG PRODUCT: Oxaliplatin for Injection

Microbiology Deficiencies:

1. With regard to buildings and facilities:

   a. Please provide floor plans for the manufacturing area(s) used for the manufacture of the subject drug product.

   b. Please provide the location (e.g. room number) of the lyophilizer(s) used in the manufacture of the subject drug product.

2. With regard to microbiological environmental monitoring:

   a. We note that (b) (4) .

   b. Please provide (b) (4) .

3. The application in 3.2.P.3.3 on Page 16 of 38 states that (b) (4)

4. With regard to the validation studies performed for the depyrogenation of closures using (b) (4)

   a. Please provide the dates of study and the amount of (b) (4) .

   b. Please describe (b) (4) .

   c. Please indicate (b) (4) .

5. With regard to equipment sterilization (b) (4)

(b) (4)

6. The manufacturing process includes (b) (4)

7. With regard to lyophilizer(s):

a. (b) (4)

b.

c.

8. With regard to media fills:

a. Please provide (b) (4)

b. Please explain (b) (4) .

c. We note that for the media fill performed on Filling Line (b) (4) on 19 DEC 05 the fill volume is stated as (b) (4) in ANDA 78-815 and (b) (4) in ANDA 78-813. Presumably, there is a typographical error. Please specify the correct fill volume.

9. With regard to the exhibit batches, we would like to verify that the parameters used for sterilization processes were supported by the validation studies. We note that the batch records cite only SOP numbers and do not provide the information we seek. This is acceptable; however, please provide either the relevant SOPs so we can verify the parameters used for the sterilization processes or else please provide a list of cycle parameters used in the exhibit batches (i.e. depyrogenation of vials, sterilization of closures, product sterilizing filters, receiving vessel, and filling equipment) and compare these to the cycle parameters used for the validation studies and to the cycle parameters proposed for commercial batches.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Brenda Pillari, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lisa Shelton
10/17/2008 06:07:15 PM
MICROBIOLOGIST

Bonnie McNeal
10/17/2008 06:16:31 PM
MICROBIOLOGIST
Checked for correct file and submission link. Both ok.

Neal Sweeney
10/21/2008 10:02:41 AM
MICROBIOLOGIST

Brenda Pillari
10/23/2008 07:18:29 AM
MICROBIOLOGIST

Product Quality Microbiology Review

January 12, 2009

ANDA: 78-815

Drug Product Name
Proprietary: N/A
Non-proprietary: Oxaliplatin for Injection
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
11/14/2008	11/17/2008	N/A	11/24/2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
02/09/2007	1	10/16/2008

Applicant/Sponsor
Name: Hospira Worldwide, Inc. (formerly Mayne Pharma Limited)
Address: 275 N. Field Dr, D-0389, Bldg. H2-2N, Lakeforest, IL 60045-5046
Representative: Laurie Wojtko, Sr. Associate, Global Regulatory Affairs
Telephone: 224-212-6158

Name of Reviewer: Lisa S.G. Shelton

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: ANDA Amendment (electronic hybrid)

2. SUBMISSION PROVIDES FOR: Response to Agency's deficiency letter

3. MANUFACTURING SITE:
Mayne Pharma Limited
1 Lexia Place
Mulgrave
Victoria 3170
Australia

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized power for injection, IV, 50 mg/vial and 100 mg/vial, packaged in a 30 mL single-use vial and 50 mL single-use vial, respectively

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Cytoxic

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: The applicant was contacted by telephone (see telecon memo dated 01/09/09) to clarify the number of lyophilizers (locations) and models used in the manufacture of the subject drug product.

filename: 78-815a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) [redacted].

B. Brief Description of Microbiology Deficiencies – None identified

C. Assessment of Risk Due to Microbiology Deficiencies –
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Lisa S.G. Shelton, Ph.D.
Microbiology Team Leader/Brenda Pillari, Ph.D.

C. CC Block
cc: Field Copy

Following this page, 13 pages withheld in full (b)(4)

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/s/

Lisa Shelton
1/13/2009 03:07:49 PM
MICROBIOLOGIST

Kun Shen
1/13/2009 04:27:01 PM
MICROBIOLOGIST

checked for correct file and linking

Neal Sweeney
1/30/2009 04:32:54 PM
MICROBIOLOGIST

Brenda Pillari
2/2/2009 06:51:24 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078815

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

VIA COURIER

February 9, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Document Control Room
Rockville, MD 20855

STERILITY ASSURANCE DATA ENCLOSED

Original Application

RE: Abbreviated New Drug Application
Oxaliplatin for Injection
(50mg/vial and 100 mg/vial)

Dear Mr. Buehler:

In accordance with the regulations, as promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act, as amended, Mayne Pharma Limited is submitting this Abbreviated New Drug Application (ANDA) for Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial.

The reference listed drug (RLD) Eloxatin® (oxaliplatin for injection), 50 mg/vial and 100 mg/vial, approved under NDA 21-492, manufactured by Sanofi Aventis, has been discontinued. Therefore, Mayne Pharma Limited makes reference to docket number 2006P-0291/CP1 filed on July 25, 2006 to determine whether Eloxatin (Oxaliplatin for Injection) has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons.

Oxaliplatin for Injection is supplied as a lyophilized, sterile powder intended for intravenous administration following reconstitution with Water for Injection available in single-dose vials containing 50 mg or 100 mg of Oxaliplatin. Each vial contains Oxaliplatin and Lactose Monohydrate, NF. Mayne's Oxaliplatin for Injection contains the same active ingredient, is of the same dosage form, is to be used for the same indications, in the same dosage regimen and via the same route of administration as the reference listed drug.

The enclosed paper application is submitted in Common Technical Document (CTD) format, as directed by relevant FDA and ICH Guidances. The application consists of the following:

Module 1: Administrative and Prescribing Information	One Volume
Module 2: Common Technical Document Summaries	One Volume
Module 3: Quality	Six Volumes
Module 4: Nonclinical Study Reports	Not Applicable
Module 5: Clinical Study Reports	Not Applicable

The proposed labeling has been submitted in electronic format, as directed by relevant Industry Guidances, and is contained on one (1) CD-ROM with the Archive Copy of this application, located in Module 1. The Quality Overall Summary is contained on one (1) CD-ROM with the Archive Copy of this application. Mayne Pharma Limited certifies that the electronic labeling and Quality Overall Summary have been scanned using Norton Symantic Antivirus Corporate Edition Version 8.1, and are virus-free.

Mayne originally submitted this application to the Division of Field Investigations on August 9, 2006. Per a January 25, 2007 phone call between myself and Irma Rivera, FDA advised that the sponsor submit a letter requesting activation of the application instead of resubmitting the entire application. On the following page is a copy of the letter to the Division of Field Investigations. In conjunction with the reactivation letter, Mayne is also submitting updated patent and exclusivity certifications, stability data and Quality Overall Summary to the Division of Field Investigations. Therefore, the application the Division of Field Investigations receives will be a true copy of that submitted for Archive and Review. Mayne is providing the Field Copy of this application to the Office of Generic Drugs Office in accordance with 21 CFR 314.94.

Mayne commits to resolve any issues identified in the methods validation process after approval of this application.

As Mayne's Authorized US Agent, should you have any questions concerning this submission, please contact me directly at (703) 566-9181.

Sincerely,

Ron Filler, MD
Authorized US Agent for Mayne Pharma Limited
Drug Development Consultants, Inc.
Tel: (703) 566-9181
Fax: (703) 566-9182

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-815

Drug Development Consultants, Inc.
U.S. Agent for Mayne Pharma Limited
Attention: Ron Filler, Ph.D.
5108 Grimm Drive
Alexandria, VA 22304

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversations dated April 26, May 2 and May 7, 2007 and your correspondence dated May 3 and May 11, 2007.

NAME OF DRUG: Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial

DATE OF APPLICATION: February 9, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 2007

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the

patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-0503.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Esther Chuh
Project Manager
301-827-5773

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
5/21/2007 11:01:22 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
** For more CTD and eCTD informational links see the final page of the ANDA Checklist
*** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ ***

ANDA #: 78-815 **FIRM NAME**: MAYNE PHARMA LIMITED

PIV: YES **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): (b) (4) [redacted]

First Generic Product Received? NO

Bio Assignments:		**Micro Review**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☐ **BDI**	

DRUG NAME: OXALIPLATIN
DOSAGE FORM: FOR INJECTION, 50 MG/VIAL AND 100 MG/VIAL

Random Queue: 2
Chem Team Leader: Smela, Michael PM: Esther Chuh Labeling Reviewer: Angela Payne

Letter Date: FEBRUARY 9, 2007	**Received Date**: FEBRUARY 9, 2007
Comments: EC -2 YES	**On Cards:** YES
Therapeutic Code: 5010100 CYTOXIC	
Archival copy: PAPER (CTD FORMAT)	**Sections** I
Review copy: YES	E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections	
PART 3 Combination Product Category N Not a Part3 Combo Product	
(Must be completed for ALL Original Applications)	Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Peter Chen	**Recommendation:**
Date 5/11/2007	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Ron Miller was informed on 5/7/2007 that the application is still missing IR spectra for batches MP103458 and MP107374.

Ron Miller was contacted again on 5/2/2007 to provide the following:

7. Please provide stability data for post-reconstitution hold time per the PI.
(OK per 5/3/2007 NC)

Ron Miller, US Agent for Mayne was contacted on 4/26/2007 to provide a response to the following items as a NC to the ANDA:

1. Please provide exclusivity statement for the M-61 exclusivity and include the expiration date with pediatric exclusivity
(OK per 5/3/2007 NC)
2. Please provide cGMP certification for the (b) (4) supplier of the API
(OK per 5/3/2007 NC)
3. Please provide IR spectra for both batches of the API, MP103458 and MP 107374.
Missing
(OK per 5/11/2007 NC)
4. Please provide a samples availability statement for the API and the drug product and include all batch numbers
(OK per 5/3/2007 NC)
5. Please provide cGMP certification for (b) (4) facility
(OK per 5/3/2007 NC)
6. Please provide a reprocessing statement for the drug product.
(OK per 5/3/2007 NC)

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: FEBRUARY 9, 2007	☒
*	**Table of Contents (paper submission only)** submitted	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) none used	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) NA	☒

1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) 5290961*PED JUL 12,2013 P4 5338874*PED OCT 07,2013 P4 5420319*PED FEB 09,2017 P4 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ No Relevant Patents ☐ 3. Expiration of Patent(s): 2/9/2017 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES but missing M-61 exclusivity (OK per 5/3/2007 NC)	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient submitted DMF (b) (4) as they said DMF submitted on 7/19/2006 Please note that there are 2 DMFs in Comis from (b) (4) for Oxaliplatin b. Type III DMF authorization letter(s) for container closure DMF (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) submitted	☒
1.12.11	**Basis for Submission** NDA# : 21-492 (DISCONTINUED IN ORANGE BOOK) DOCKET NO. 2006P-0291 Ref Listed Drug: ELOXATIN (for injection) Firm: SANOFI AVENTIS ANDA suitability petition required? If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Same as RLD 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) submitted **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained submitted **1.14.1.3** 1 package insert (content of labeling) submitted electronically submitted ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted **1.14.3.3** 1 RLD label and 1 RLD container label submitted	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __X_PDF (archive) _X_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _X__ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature submitted** **3.2.S.1.2** **Structure submitted** **3.2.S.1.3** **General Properties submitted**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers submitted 2. Manufacturing Responsibilities submitted 3. Type II DMF number for API submitted 4. CFN or FEI numbers Missing cGMP statement for (b) (4) (OK per 5/3/2007 NC)	☒
3.2.S.3	**Characterization submitted and Reference to DMF**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) submitted **3.2.S.4.2** **Analytical Procedures** submitted **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples missing Spectra for Both API batches (one provided is for a different batch than the ones used for this ANDA) (OK per 5/11/2007 NC) 2. Samples-Statement of Availability and Identification of: a. Drug Substance missing (OK per 5/3/2007 NC) b. Same lot number(s) **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) submitted Batch # 10802, 10902 2. Applicant certificate of analysis submitted Batch # MP103458 and MP 107374 **3.2.S.4.5** **Justification of Specification submitted**	☒
3.2.S.5	**Reference Standards or Materials submitted**	☒
3.2.S.6	**Container Closure Systems Reference to DMF**	☒
3.2.S.7	**Stability Reference to DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition submitted 2) Inactive ingredients are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report submitted	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) submitted 2. CGMP Certification: submitted but missing for [redacted] (b) (4) testing facility 3. Function or Responsibility submitted 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation submitted **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process submitted 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 50 mg vials MBR TY [redacted] (b) (4) 100 mg vials MBR TY [redacted] (b) (4) 3. If sterile product: [redacted] (b) (4) 4. Reprocessing Statement missing (OK per 5/3/2007 NC) **3.2.P.3.4** **Controls of Critical Steps and Intermediates submitted** **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation submitted 2. [redacted] (b) (4) submitted per Paul D. vol 1.4	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified submitted **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) submitted 2. Suppliers' COA (specifications and test results) submitted **3.2.P.4.2** **Analytical Procedures per USP/NF** **3.2.P.4.3** **Validation of Analytical Procedures per USP/NF** **3.2.P.4.4** **Justification of Specifications** Applicant COA submitted	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** submitted **3.2.P.5.2** **Analytical Procedures** submitted **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form missing (OK per 5/3/2007 NC) 2. Same lot numbers **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form submitted 50 mg vials Batch #N015350R 100 mg vials Batch #N025352R **3.2.P.5.5** **Characterization of Impurities reference to another section** **3.2.P.5.6** **Justification of Specifications submitted**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted 3. Packaging Configuration and Sizes 50 mg and 100 mg vials 4. Container/Closure Testing submitted 5. Source of supply and suppliers address submitted	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted submitted 2. Expiration Dating Period 24 months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments submitted **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data submitted post reconstitution stability data provided in section 3.2.P.2.6.1 2. Batch numbers on stability records the same as the test batch **yes**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 50 mg vials Batch #N015350R: TY (b) (4) PY (b) (4) 100 mg vials Batch #N025352R: TY (b) (4) PY (b) (4) **3.2.R.1.P.2** **Information on Components** none submitted **3.2.R.2.P** **Comparability Protocols** none submitted **3.2.R.3.P** **Methods Validation Package** submitted Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina

Search results from the "OB_Disc" table for query on "021492."

Active Ingredient:	OXALIPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	ELOXATIN
Applicant:	SANOFI AVENTIS US
Strength:	50MG/VIAL
Application Number:	021492
Product Number:	001
Approval Date:	Aug 9, 2002
RX/OTC/DISCN:	DISCN
Patent and Exclusivity Info for this product:	View

Active Ingredient:	OXALIPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	ELOXATIN
Applicant:	SANOFI AVENTIS US
Strength:	100MG/VIAL
Application Number:	021492
Product Number:	002
Approval Date:	Aug 9, 2002
RX/OTC/DISCN:	DISCN
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through March, 2007
Patent and Generic Drug Product Data Last Updated: April 25, 2007

Patent and Exclusivity Search Results from query on Appl No 021492 Product 001 in the OB_Disc list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021492	001	5290961	JAN 12,2013			
021492	001	5290961*PED	JUL 12,2013			
021492	001	5338874	APR 07,2013	Y		
021492	001	5338874*PED	OCT 07,2013			
021492	001	5420319	AUG 09,2016	Y		
021492	001	5420319*PED	FEB 09,2017			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021492	001	PED	JUL 09,2007
021492	001	I-441	NOV 04,2007
021492	001	I-425	JAN 09,2007
021492	001	PED	MAY 04,2008
021492	001	PED	JUL 10,2010
021492	001	M-61	JAN 10,2010
021492	001	NCE	AUG 09,2007
021492	001	PED	FEB 09,2008

Patent and Exclusivity Search Results from query on Appl No 021492 Product 002 in the OB_Disc list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021492	002	5290961	JAN 12,2013			
021492	002	5290961*PED	JUL 12,2013			
021492	002	5338874	APR 07,2013	Y		
021492	002	5338874*PED	OCT 07,2013			
021492	002	5420319	AUG 09,2016	Y		
021492	002	5420319*PED	FEB 09,2017			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021492	002	PED	JUL 09,2007
021492	002	PED	MAY 04,2008
021492	002	I-425	JAN 09,2007
021492	002	PED	FEB 09,2008
021492	002	PED	JUL 10,2010
021492	002	I-441	NOV 04,2007
021492	002	NCE	AUG 09,2007
021492	002	M-61	JAN 10,2010

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

/s/

Martin Shimer

5/21/2007 10:58:40 AM

Drug Development Consultants, Inc.

5108 Grimm Drive
Alexandria, Virginia 22304
T/F: (703) 566-9181/9182
e-mail: ddci.rf@comcast.net

ORIGINAL

VIA COURIER

7 August 2007

76815

N/mc

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park Two (MPN-2)
7500 Standish Place
Rockville, MD 20855

Attention: Document Room

Re: Abbreviated New Drug Applications 78-813 and 78-815
Amendments to Pending Applications; Notice of Filing of Legal Action

Dear Sir:

In accordance with 21 C.F.R. § 314.95(e), Mayne Pharma Limited requests amendment of each of its Abbreviated New Drug Applications ("ANDAs") 78-813 and 78-815 to document receipt of the respective notice of certification required under § 314.95(a) by each person to whom the notice was provided.

Enclosed herewith are copies of the return receipt postcards evidencing the fact that the each of the approved NDA holder and the patent owner, as defined in § 314.95(a), properly received the notice of certification for each of ANDAs 78-813 and 78-815 between June 11-13, 2007. Also enclosed herewith are respective Forms FDA 356h, clarifying that these materials are being submitted as Amendments to Pending Applications.

In accordance with 21 C.F.R. § 314.107(f), Mayne Pharma Limited is also providing notice to FDA of the filing of a lawsuit by Sanofi-Aventis, Sanofi-Aventis U.S. LLC (the NDA holder), and Debiopharm, S.A. (the patent owner) against Mayne Pharma Limited on July 23, 2007 (Case No. 3:07-cv-03409, District of New Jersey) relating to both of the ANDAs 78-813 and 78-815. Enclosed herewith is a copy of the docket sheet for the above-referenced lawsuit.

As Mayne's Authorized US agent, should you have any questions concerning this submission, please contact me directly at 1-703-566-9181.

Sincerely,

Ron Filler, Ph.D.
Authorized US Agent for Mayne Pharma Limited
Drug Development Consultants, Inc.
Tel: (703) 566-9181
Fax: (703) 566-9182

Enclosures

Hospira

14th August, 2007

N/mc

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park Four
7500 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application 78-815

Dear Sir:

Hospira Australia Pty Ltd authorizes Drug Development Consultants, Inc. to act as United States Agent for the purposes of this application including, but not limited to, signing agency correspondence and patent certifications and related documents.

Contact information for this Agent is below:

Ron Filler, Ph.D.
Drug Development Consultants, Inc.
5108 Grimm Drive
Alexandria, VA 22304
Phone: 703-566-9181
Fax: 703-566-9182
Email: ddci.rf@comcast.net

Sincerely,

Geraldine Storton
Regional Director of Regulatory Affairs, APAC
Hospira Australia Pty Ltd

Hospira Australia Pty Ltd
ABN 58 097 064 330
551 Blackburn Road
Mt Waverley Victoria 3149
P O Box 394 Mulgrave North
Victoria 3170 Australia
Telephone +61 3 8541 5200
Facsimile +61 3 8541 5790
www.maynepharma.com

MINOR AMENDMENT

ANDA 78-815

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Drug Development Consultants, Inc.
U. S. Agent for Mayne Pharma Limited TEL: 703-566-9181

ATTN: Ron Filler FAX: 703-566-9182

FROM: Esther Chuh PROJECT MANAGER: (301) 827-5773

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated February 9, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-815

APPLICANT: Mayne Pharma Limited

DRUG PRODUCT: Oxaliplatin Lyophilized Powder for Injection, 50 mg and 100 mg per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF (b) (4) is deficient and the DMF holder has been notified. Please ensure a response.

2. Please express the (b) (4) .

3. Please include (b) (4)

4. Please include (b) (4)

5. We acknowledge that you use (b) (4)

6. As part of the in-process control, please include (b) (4) .

7. Please include (b) (4)

8. You have proposed (b) (4)

9. Please revise (b) (4) .

10. We acknowledge that you use (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your labeling and microbiological information are pending review. Deficiencies, if any will be communicated separately.

2. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

3. There appears to be a typographical error in reporting the [redacted] on Table 4.6.1 (p. 12 of 29). It should have been [redacted] instead of [redacted]. Please confirm.

4. You have reported the Maximum Daily Dose (MDD) of the drug product as 234 mg (= 130 mg/m^2 x 1.8 m^2). Please note that MDD should have been reported as 147 mg (= 85 mg/m^2 x 1.73 m^2).

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Michael Smela
8/22/2007 04:03:37 PM
For Rashmikant M. Patel, Ph.D.

VIA COURIER

23 August 2007

N/XA

Attn Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
Document Control Room
7500 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application 78-815, Oxaliplatin for Injection

NOTICE OF COMPANY NAME CHANGE

Dear Sir:

Mayne Pharma Limited is hereby forwarding to its Abbreviated New Drug Application ("ANDA") 78-815, notification of a change to company name. Effective as of August 7th, 2007, the company name, Mayne Pharma Limited, was changed to Hospira Australia Pty Ltd. The name change affects both the name of the applicant as well as the manufacturing site. All other relevant company details, including site addresses and other contact information, remain the same.

Enclosed herewith is a revised Form FDA 356h reflecting the updated company name. Changes to proposed product labeling to reflect the Hospira brand, will be effected during the review cycle of the application through deficiency responses.

There is no change to the company's US Agent, however an updated Letter of Authorization reflecting that Drug Development Consultants, Inc will continue to act on behalf of Hospira Australia Pty Ltd, is also provided.

As Hospira's Authorized US agent, should you have any questions concerning this submission, please contact me directly at 1-703-566-9181.

Sincerely,

Ron Filler, Ph.D.
Authorized US Agent for Hospira Australia Pty Ltd
Drug Development Consultants, Inc.
Tel: (703) 566-9181
Fax: (703) 566-9182
e-mail: ddci.rf@comcast.net

Enclosures

Record of Telephone Conversation

Reference is made to the Chemistry Deficiency sent out to the firm on 8/22/2007. The firm requested for clarification on #3 of the deficiency:

FDA Deficiency:
Please include (b) (4) .

Firm's Question:
Is agency interested in (b) (4) ?

Agency's Answer:
We are interested in (b) (4)

Date:
9/13/2007

ANDA Number
78-813
78-815

Product Name:
Oxaliplatin Injection, 5 mg/mL, 10 mL and 20 mL vials
Oxaliplatin Lyophilized Powder for Injection, 50 mg and 100 mg per vial

Firm Name:
Mayne Pharma Limited

Firm Representative:
Ron Filler

Phone Number:
703-566-9182

FDA Representative:
Mike Smela
Esther Chuh

Signatures:

Mike Smela

Esther Chuh

CC: DFS ANDA 77813, 77815
Chem Division I, T-Con Notebook

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

/s/

Esther Chuh
9/14/2007 02:24:59 PM
CSO

Michael Smela
9/14/2007 02:34:24 PM
CHEMIST

Citation to new DMF and batch data. Convert to MAJOR amendment
H Smale 12/10/07

VIA COURIER

November 26, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Metro Park North II
Rockville, MD 20855

ORIG AMENDMENT

N/AC

Re: ANDA 78-815 Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial

MINOR AMENDMENT - RESPONSE TO CHEMISTRY DEFICIENCIES
GRATUITOUS AMENDMENT - ADDITION OF AN ALTERNATE DRUG SUBSTANCE MANUFACTURING PROCESS

Dear Mr. Buehler:

Hospira Australia Pty Ltd. hereby amends the above-referenced abbreviated new drug application Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial, ANDA 78-815, submitted on February 9, 2007. We are responding to the Agency's chemistry deficiencies letter dated August 22, 2007. This amendment serves as the response to the chemistry deficiencies. Provided in Exhibit 1 are the Agency's comments with Hospira's responses.

Additionally, in accordance with 21 C.F.R. § 314.96, Hospira Australia Pty Ltd. hereby requests amendment of its ANDA 78-815 to add an alternate manufacturing process for oxaliplatin drug substance. This gratuitous amendment is provided in Exhibit 2.

Exhibit 2 includes information and data regarding the drug substance oxaliplatin, manufactured using an alternative process. The drug substance manufacturer, (b) (4) remains the same, and the difference in process from that originally submitted is minor. The alternate process drug substance (b) (4) is supported by a separate Drug Master File (DMF) # (b) (4).

One batch each of the 50 mg/vial and 100 mg/vial presentations has been manufactured using the (b) (4) drug substance, and batch analysis data and batch records are provided to support this gratuitous amendment. Given that the change to the drug substance manufacturing process is minor, and that the physicochemical properties, including that the impurity profile of the drug substance is identical to the original process, no drug product stability data has been provided. The drug product batch analysis data

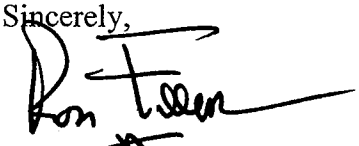
demonstrates that the alternate process produces an equivalent drug product. Since the drug substance stability is inherent, it is considered that batch analysis is sufficient to demonstrate that the change to drug substance will have no impact on the quality, safety or efficacy of the resultant drug product. The company commits to placing one (1) batch per presentation on stability and providing the stability data. Refer to Table 1 of Exhibit 2 for a tabulated summary of information provided supporting this gratuitous amendment.

Please note that the company name was changed from Mayne Pharma Limited to Hospira Australia Pty Ltd. The change was effective from August 7, 2007. Consequently, some documentation supporting this amendment reflects the previous company name. In these instances, references to Mayne Pharma Limited should be considered as Hospira Australia Pty Ltd. Section 3.2.P.3.1 has been revised and included in Exhibit 2.

Hospira Australia Pty Ltd. is providing an Archive and Review Copy of this submission to the Office of Generic Drugs. A Field Copy is also being submitted to the Office of Generic Drugs. Hospira Australia Pty Ltd. certifies that the Field Copy is a true copy of the information contained in the Review and Archive Copies.

As Hospira Australia's Authorized US Agent, should you have any questions concerning this submission, please contact me directly at 1-703-566-9181.

Sincerely,



Ron Filler, Ph.D.
Authorized US Agent for Hospira Australia Pty Ltd.
Drug Development Consultants, Inc.
Tel: (703) 566-9181
Fax: (703) 566-9182

Enclosures

Hospira

December 24, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Central Document Room
Rockville, MD 20855

NJ/NR

RE: ANDA 78-815 Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial

Gratuitous Amendment

Dear Mr. Buehler:

A gratuitous amendment is being submitted to this ANDA application to change its US Agent from Drug Development Consultants. Inc. to Hospira, Inc.

Hospira Australia Pty. Ltd. hereby authorizes Hospira, Inc to act as its United States Agent for the purposes of this application including, but not limited to, signing agency correspondence and patent certifications and related documents.

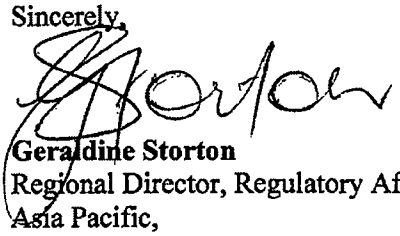
Contact information for this Agent is below:

Judith Zutkis
Director, Global Regulatory Affairs
Hospira, Inc.
275 North filed Drive
Lake Forest, IL 60045
Tel: (224) 212-4949
Fax: (224) 212-5401
Email: judith.zutkis@hospira.com

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60064

Hospira

Sincerely,



Geraldine Storton
Regional Director, Regulatory Affairs
Asia Pacific,
Hospira Australia Pty. Ltd.

Telephone Fax

ANDA 78-815

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Mayne Pharma

TEL: 201-225-5514

ATTN: Steve Richardson

FAX: 201-225-5530

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin for Injection.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-815 Date of Submission: 09 FEB 2007 (Original)
Applicant's Name: Mayne Pharma
Established Name: Oxaliplatin for Injection 50 mg and 100 mg per vial- PF-SDV, Lyophilized

---

Labeling Deficiencies: Firm submitted e-draft.

1. CONTAINER

a. We encourage you to add “cytotoxic agent” to your labels.

b. List the in actives under an "inactive" category.

We are aware that the innovator uses tall man lettering as part of the established name. However, upon further review this product should not display tall man lettering. We acknowledge you have revised without regard for tall man lettering and have displayed "Oxaliplatin" rather than "OXALIplatin" and we find that acceptable.

2. CARTON -See comments under CONTAINER.

3. INSERT - Minor correction in the Highlighted section, second paragraph - revise "….. powder for solution for intravenous…".

4. PATIENT INFORMATION SHEET - Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed or draft electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
3/16/2008 04:58:54 PM
for Wm Peter Rickman

MINOR AMENDMENT

ANDA 78-815

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Hospira, Inc. TEL: 224-212-4949

ATTN: Zudith Zutkis, Director, Regulatory Affairs FAX: 224-212-5401

FROM: Esther Chuh PROJECT MANAGER: (240)276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated February 9, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial.

Reference is made to your amendment dated November 26, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-815

APPLICANT: Hospira Australia Pty Ltd.

DRUG PRODUCT: Oxaliplatin Lyophilized Powder for Injection, 50 mg and 100 mg per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF (b) (4) is deficient and the DMF holder has been notified. Please ensure a response.

2. Your proposed (b) (4)

3. You proposed not to (b) (4)

4. The limit for the Uniformity of content test in the release specifications should be stated as "Complies with USP <905>".

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your labeling information has been reviewed and deficiencies have been communicated to you. Please respond to the deficiencies.

2. Your microbiological information is pending review. Deficiencies, if any, will be communicated separately.

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Michael Smela
5/20/2008 03:09:18 PM
For Rashmikant M. Patel, Ph.D.

Hospira

August 1, 2008

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
Document Room
7500 Standish Place
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial

MINOR AMENDMENT – RESPONSE TO CHEMISTRY DEFICIENCIES

Dear Mr. Buehler,

Hospira, Inc. hereby submits a chemistry amendment to the above-referenced abbreviated new drug application in response to the Agency's comments in the correspondence received on May 20, 2008.

The Agency's comments and Hospira's responses to these comments in MS Word compatible format are contained in the CD attached. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@secure.hospira.com

RECORD OF TELEPHONE CONVERSATION

FDA:

The firm was told the following:

- The drug product release specification should be revised to include "Residual Solvents" with the acceptance criteria as "Complies with USP <467>".
- The vendor's statement regarding the solvents used in the manufacture of Lactose monohydrate need to be revised and add test to your acceptance criteria if any are used.
- Commitment needed from the applicant to re-evaluate <467> if they change suppliers of excipients.

End of the T-CON.

Date: August 29, 2008

ANDA NUMBER: 78-815

PRODUCT NAME:
Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

INITIATED BY:

FIRM __ FDA _X_

FIRM NAME:
Hospira Worldwide, Inc.

FIRM REPRESENTATIVE:
Laurie Wojtko

TELEPHONE NUMBER:
224-212-6158

FDA REPRESENTATIVE:
Bita Mirzai-Azarm (Chem Reviewer)

SIGNATURE

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

/s/

Bita Mirzai-Azarm
8/29/2008 11:14:34 AM
CHEMIST

Hospira

September 4, 2008

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
Document Room
7500 Standish Place
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial

GRATUITOUS AMENDMENT – COMPLIANCE WITH USP <467> RESIDUAL SOLVENTS

Dear Mr. Buehler,

Hospira, Inc. hereby submits a gratuitous chemistry amendment to the above-referenced abbreviated new drug application in order to comply with the General Chapter of the USP for Residual Solvents <467> that took effect on July 1, 2008. Hospira commits to re-evaluate the drug substance and excipients for residual solvents as a result of any future supplier change.

The amendment in MS Word compatible format is contained in the CD attached. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko 9-4-08

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@secure.hospira.com

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (240-276-8408)

TO: Ron Filler		**FROM:** Kun Shen
Hospira Australia Pty Ltd		Microbiology Project Manager
PHONE: 703-566-9181		**PHONE:** (240) 276-8722
FAX: 703-566-9182		**FAX:** (240) 276-8725

Total number of pages, excluding this cover sheet: 4

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 78-815, Oxaliplatin for Injection. The submission reviewed was submitted on February 9, 2007. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Kun Shen, Bonnie McNeal or Mark Anderson.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 78-815 APPLICANT: Hospira Australia Pty Ltd

DRUG PRODUCT: Oxaliplatin for Injection

Microbiology Deficiencies:

1. With regard to buildings and facilities:

   a. Please provide floor plans for the manufacturing area(s) used for the manufacture of the subject drug product.

   b. Please provide the location (e.g. room number) of the lyophilizer(s) used in the manufacture of the subject drug product.

2. With regard to microbiological environmental monitoring:

   a. We note that (b) (4) .

   b. Please provide (b) (4) .

3. The application in 3.2.P.3.3 on Page 16 of 38 states that (b) (4)

4. With regard to the validation studies performed for the depyrogenation of closures using (b) (4) :

   a. Please provide the dates of study and the amount o (b) (4)

   b. Please describe (b) (4) .

   c. Please indicate (b) (4) .

5. With regard to equipment sterilization in [redacted] (b) (4)

6. The manufacturing process includes [redacted] (b) (4)

7. With regard to lyophilizer(s):

   a. [redacted] (b) (4)

   b.

   c.

8. With regard to media fills:

   a. Please provide [redacted] (b) (4)

   b. Please explain [redacted] (b) (4)

   c. We note that for the media fill performed on Filling Line [redacted] (b) (4) on 19 DEC 05 the fill volume is stated as [redacted] (b) (4) in ANDA 78-815 and [redacted] (b) (4) in ANDA 78-

813. Presumably, there is a typographical error. Please specify the correct fill volume.

9. With regard to the exhibit batches, we would like to verify that the parameters used for sterilization processes were supported by the validation studies. We note that the batch records cite only SOP numbers and do not provide the information we seek. This is acceptable; however, please provide either the relevant SOPs so we can verify the parameters used for the sterilization processes or else please provide a list of cycle parameters used in the exhibit batches (i.e. depyrogenation of vials, sterilization of closures, product sterilizing filters, receiving vessel, and filling equipment) and compare these to the cycle parameters used for the validation studies and to the cycle parameters proposed for commercial batches.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Brenda Pillari, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Brenda Pillari

10/23/2008 10:59:33 AM

November 3, 2008

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
Document Room
7500 Standish Place
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial

MINOR AMENDMENT – RESPONSE TO LABELING DEFICIENCIES

Dear Mr. Buehler,

Hospira, Inc. hereby submits a labeling amendment to the above-referenced abbreviated new drug application in response to the Agency's comments in the correspondence dated on March 24, 2008. The Agency's comments and Hospira's responses to these comments in MS Word compatible format are contained in the CD attached.

The CD also contains electronic content of labeling as FPL, and the side-by-side comparisons of the revised package insert to the approved innovator's labeling components, and container and carton labeling components to the previously submitted labeling components. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@hospira.com

Hospira

November 14, 2008

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Electronic Hybrid Submission

Microbiology/Sterility Assurance Documentation Enclosed

Re: Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial
ANDA 78-815

MINOR AMENDMENT--RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Mr. Buehler:

Hospira, Inc. hereby amends the above-referenced abbreviated new drug application for Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial, ANDA 78-815. We are responding to the Agency's microbiology deficiencies sent on October 28, 2008. This amendment serves as the response to the microbiology deficiencies. Attached are the Agency's comments with Hospira's responses.

On February 2, 2007 Hospira, Inc. acquired Mayne Pharma Limited. This original ANDA applies to Hospira, Inc. In those instances herein where there is a reference to Mayne Pharma (USA), Inc. or Mayne Pharma Limited, this should be considered as applying to Hospira, Inc.

The Agency's comments and Hospira's responses to these comments in MS Word compatible format are contained on the CD attached. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,
HOSPIRA, INC.

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: laurie.wojtko@hospira.com

Hospira

November 19, 2008

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
Document Room
7500 Standish Place
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial

GRATUITOUS LABELING AMENDMENT

Dear Mr. Buehler,

Hospira, Inc. hereby re-submits a labeling amendment to the above-referenced abbreviated new drug application in response to the request from the labeling reviewer, Ms. Angela Payne on November 18, 2008. According to Ms. Payne, the labeling files previously sent on November 3, 2008 could not be opened and used as required. Therefore, another copy of the labeling amendment with all associated files related to the deficiency response is provided.

The CD also contains electronic content of labeling as FPL, and the side-by-side comparisons of the revised package insert to the approved innovator's labeling components, and container and carton labeling components to the previously submitted labeling components. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

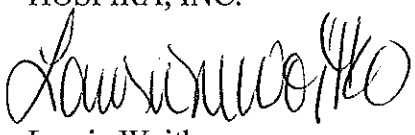
Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.



Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@hospira.com

RECORD OF TELEPHONE CONVERSATION

FDA:

The applicant was asked to provide a commitment that their DS specs will be revised based on the Pharmacopeial Forum (PF) 34(4) In-Process Revision for Oxaliplatin. In addition, to contact the DMF holder.

End of the T-CON.

Date: 02-FEB-2009

ANDA NUMBER: 78-815

PRODUCT NAME:
Oxaliplatin Lyophilized Powder for Injection, 50 mg/vial and 100 mg/vial

INITIATED BY:

FIRM __ FDA _X_

FIRM NAME:
Hospira Worldwide, Inc.

FIRM REPRESENTATIVE:
Laurie Wojtko

TELEPHONE NUMBER:
224-212-6158

FDA REPRESENTATIVE:
Bita Mirzai-Azarm (Acting TL)

SIGNATURE

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

/s/

Bita Mirzai-Azarm

2/2/2009 10:36:16 AM

CHEMIST

FEB 0 3 2009

Hospira

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial

TELEPHONE AMENDMENT - LABELING

Dear Mr. Buehler,

Hospira, Inc. hereby submits a labeling amendment to the above-referenced abbreviated new drug application in response to the request from the labeling reviewer, Ms. Angela Payne on January 14, 2008. According to Ms. Payne, the product insert amended on November 3, 2008 contained three figures that were not well resolved. Therefore, the product insert labeling files, including pdf, word, and SPL, have been updated to address the resolution issue and resubmitted herein.

This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko 2-3-09

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@hospira.com

Hospira

February 5, 2009

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/Vial, 100 mg/Vial

TELEPHONE AMENDMENT - CHEMISTRY

Dear Mr. Buehler,

Hospira, Inc. hereby submits a telephone amendment to the above-referenced abbreviated new drug application in response to a request from the chemistry reviewer, Ms. Bita Mirzai-Azam on January 30, 2009. Ms. Mirzai-Azam has requested that a commitment be provided as it relates to the pending drug substance monograph for Oxaliplatin in the Pharmacopeial Forum 34 (4). A commitment has been provided herein.

This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko 2-5-09

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
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E-mail: Laurie.Wojtko@hospira.com

Telephone Fax

ANDA 78-815

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Mayne Pharma

TEL: 201-225-5514

ATTN: Steve Richardson

FAX: 201-225-5530

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin for Injection.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-815 Date of Submission: 03 NOV 2008 and 19 NOV 2008

Applicant's Name: Mayne Pharma

Established Name: Oxaliplatin for Injection 50 mg and 100 mg per vial- PF-SDV, Lyophilized

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Labeling Deficiencies:

1. **CONTAINER -** Satisfactory.
2. **CARTON** - Satisfactory.
3. **INSERT -** Please increase the resolution of the text to improve upon the tables and graphs as expressed in my recent telephone communication with you. Please resubmit.
4. **PATIENT INFORMATION SHEET -** Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed or draft electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
2/6/2009 12:22:56 PM
for Wm Peter Rickman

Hospira

APR 29 2009

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
Document Room
7500 Standish Place
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin Injection, 50 mg/Vial, 100 mg/Vial

GRATUITOUS AMENDMENT – LABELING

Dear Mr. Buehler,

Hospira, Inc. hereby submits a labeling amendment to the above-referenced abbreviated new drug application in response to a labeling revision by the reference listed drug Sanofi-Aventis' Eloxatin which was approved on March 13, 2009.

The CD also contains electronic content of labeling as FPL, and the side-by-side comparisons of the revised package insert to the approved innovator's labeling components. This amendment is submitted as an electronic hybrid which does not contain an XML backbone. The CTD sections are bookmarked and hyperlinked. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.0 virus scanning software.

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko 4-28-09

Laurie Wojtko
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Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@hospira.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 22 2009

Mr. Mark Moyer
Vice President, U.S. Deputy Head, Regulatory Development
Sanofi-Aventis US LLC, a subsidiary of Sanofi-Aventis
9 Great Valley Parkway
Malvern, PA 19355-1304

Re: Docket No. FDA-2006-P-0025

Dear Mr. Moyer:

This letter responds to your petition dated December 19, 2006 (Petition), and supplements to that petition dated April 23, 2007 (First Supplement) and April 28, 2009 (Second Supplement).[1] You request that the Food and Drug Administration (FDA) give special consideration for any abbreviated new drug application (ANDA) referencing Eloxatin (oxaliplatin injection) containing added acid (other than oxalic acid), or conjugate base thereof, or containing an added sugar or sugars (e.g., lactose). You also request that FDA require such an application to demonstrate through sufficient preclinical and/or clinical testing that any new compound resulting from the addition of an added acid, or its conjugate base, or an added sugar to oxaliplatin does not compromise the safety or efficacy of the drug product.

For the reasons that follow, your petition and supplements are granted to the extent described and are otherwise denied.

I. BACKGROUND

Eloxatin is a platinum compound approved for the adjuvant treatment of stage III colon cancer and for the treatment of advanced colorectal cancer. Eloxatin is approved in two dosage forms: (1) a lyophilized powder that is reconstituted for injection, containing lactose, which has been withdrawn from sale (new drug application (NDA) No. 21-492) and is listed in the "Discontinued Drug Product List" section of FDA's *Approved Drug Products with Therapeutic Equivalence* Evaluation (Orange Book) (27th ed.),[2] and (2) an aqueous solution that contains neither added acid (or its conjugate base) nor added sugar (NDA No. 21-759). The subject of this petition is the currently marketed Eloxatin aqueous solution.

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[1] This citizen petition was originally assigned docket number 2006P-0523/CP1. The number was changed to FDA-2006-P-0025 as a result of FDA's transition to its new docket numbering system (Regulations.gov) in January 2008.

[2] FDA determined that this product was not withdrawn from marketing for reasons of safety or effectiveness (72 FR 65968, November 26, 2007).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD and that it has the same active ingredient or ingredients, dosage form, route of administration, strength, and labeling[3] as the RLD. The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the following conditions are therapeutically equivalent and may be substituted for each other: (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity, and identity, and are manufactured in compliance with Current Good Manufacturing Practices regulations; and (3) are adequately labeled.

II. DISCUSSION

A. Review Under an ANDA Versus NDA

1. Added acid (other than oxalic acid) or its conjugate base

You state that because an application for generic oxaliplatin solution with an added acid, or conjugate base thereof, must contain necessary preclinical and/or clinical data, submission of an ANDA under section 505(j) of the Act would not be appropriate and that instead, the generic applicant must submit to FDA an NDA under section 505(b) of the Act (Petition at 3 and 12-13, citing section 505(j)(2)(C)(i) of the Act).

As a threshold matter, we think it is important to review the requirements for an ANDA for a parenteral drug product. A drug product intended for parenteral use generally must contain both the same active and inactive ingredients in the same concentration as the reference listed drug. There is, however, the following exception for differences in inactive ingredients under 21 CFR 314.94(a)(9)(iii):

> An applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

[3] An ANDA must contain the same drug product labeling as the RLD, except for differences approved under a suitability petition, or differences required because the proposed drug product and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the Act and 21 CFR 314.94(a)(8)).

A buffer consists of a weak acid and its conjugate base. Therefore, inactive ingredients consisting of an acid and its conjugate base functioning as a buffer meet the exception for a buffer under 21 CFR 314.94(a)(9)(iii). Accordingly, FDA would accept for review an ANDA for generic oxaliplatin solution that contains an added buffer in the form of an acid (other than oxalic acid), or conjugate base thereof (buffered oxaliplatin), citing Eloxatin solution as the reference listed drug. An applicant would need to provide evidence that this buffer does not affect the safety or efficacy of the generic oxaliplatin solution.

We discuss in section II.B.1 of this document the circumstances under which we would require additional preclinical and/or clinical data to demonstrate that any new compound resulting from the addition of an added acid, or its conjugate base, does not compromise the safety or efficacy of the drug product. If clinical data were required, as you suggest, FDA would not review the application for generic buffered oxaliplatin solution under section 505(j) of the Act, but instead, would require that application to be submitted under section 505(b) of the Act. However, if FDA determined that preclinical data (e.g., toxicological studies, comparative preclinical studies) would be sufficient and clinical data is not necessary, FDA would review the generic application under section 505(j) of the Act.

2. Added sugar

You assert that because an application for generic oxaliplatin solution with added sugar or sugars must contain necessary preclinical and/or clinical data, submission of an ANDA is not appropriate and the application must be submitted as an NDA under section 505(b) of the Act (First Supplement at 12).

FDA agrees that an application referencing the aqueous form of Eloxatin that contained an added sugar must be submitted under section 505(b) of the Act. As discussed in section II.A.1 of this document, as a condition for ANDA approval of a drug product intended for parenteral use, the generic formulation must contain both the same active and inactive ingredients in the same concentration as the innovator's formulation, with the exception for preservative, buffer, or antioxidant described in 21 CFR 314.94(a)(9)(iii). Because an added sugar does not meet the definition of a preservative, buffer, or antioxidant in the exception, FDA would not accept for review an ANDA for a generic oxaliplatin solution that contains an added sugar, citing Eloxatin solution as the RLD. Under these circumstances, an application for oxaliplatin solution with an added sugar could be submitted under section 505(b)(2) of the Act. [4]

As discussed in section II.B.2 of this document, the criteria for evaluating whether preclinical and/or clinical data may be necessary to ensure the safety and efficacy of any new platinum complex that may contain a by-product (i.e., degradation product,

[4] An application described in section 505(b)(2) of the Act relies upon investigations described in section 505(b)(I)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

degradation impurity) as the result of the added sugar are the same for an ANDA submission as for an NDA submission.

B. Necessity for Preclinical/Clinical Trials to Demonstrate Safety and/or Efficacy

1. Added acid (other than oxalic acid) or its conjugate base

You state that FDA must require any ANDA referencing Eloxatin to contain data from preclinical and/or clinical testing sufficient to demonstrate that the addition of an acid (other than oxalic acid), or conjugate base thereof, does not significantly alter the safety or efficacy profile of the resulting product (Petition at 12-13). Specifically, you state that adding an acid (other than oxalic acid), or its conjugate base, to buffer the oxaliplatin solution may cause the formation of new platinum compounds (Petition at 6). You state that the platinum complexes resulting from these formulation changes may contain a new by-product (i.e., degradation product, degradation impurity) that may affect safety and/or efficacy (Petition at 6-12, citing Dr. Chaney, Dr. Farrell, other authors, and other literature). As an example, you state that a new platinum complex, tartaroplatin, is formed as a result of ligand exchange when tartaric acid is added to oxaliplatin (Petition at 10-11). In the recently submitted Second Supplement, you reported on an effort to analyze impurities present in a generic product containing tartaric acid approved in Europe.

We agree that:

- Adding an acid (other than oxalic acid), or its conjugate base, to buffer the oxaliplatin solution may result in the formation of new platinum complexes under anticipated storage conditions. Oxaliplatin formulations containing an added buffer may undergo chemical exchange reactions in which the conjugate base of the acid displaces the oxalate ligand bound to platinum, forming a new platinum complex.

- New platinum complexes may have an impact on the safety and/or efficacy of the drug product.[5] Therefore, preclinical and/or clinical studies may be necessary if significant amounts of new platinum complexes occur under anticipated storage and use conditions.

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[5] For example, by-products may have a leaving group ligand bound to platinum that is different from the oxalate leaving group ligand in oxaliplatin. The rate of substitution of this leaving group ligand, in part, affects biological activity and toxicity. By-products with leaving group ligands having fast dissociation rates may give rise to highly toxic complexes (e.g., diaquoPt(DACH)). Conversely, by-products with leaving group ligands having slow disassociation rates may yield inactive and nontoxic complexes (Schwartz, P., et al., "Preparation and antitumor evaluation of water-soluble derivatives of dichloro(1,2-diaminocyclohexane)platinum(II)," *Cancer Treatment Reports* (1977) 61:1519-1525; Cleare, M.J., et al., "Studies on the antitumor activity of Group VIII transition metal complexes. Part I. Platinum(II) complexes," *Bioinorganic Chemistry* (1973) 2:187-210).

- Potential biological activity and toxicity of new platinum complexes cannot be predicted based solely on the determination of structural similarity to other platinum-containing drug products.

However, preclinical and/or clinical studies may not be necessary to demonstrate that an added acid, or its conjugate base, has an impact on the safety or efficacy profile of the resulting oxaliplatin drug product. The need for preclinical and/or clinical safety evaluation is dependent, in part, upon the extent to which new degradation impurities are formed in the product formulation during storage.

Each ANDA or NDA applicant must satisfy various requirements, including the standards for chemistry, manufacturing, and controls (CMC). The purpose of the CMC review is to ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are adequate to assure and preserve its identity, strength, purity, and quality (21 CFR 314.127(a)(l); section 505(j)(4)(A) of the Act). ANDA applicants must submit, with one exception not relevant here, the same type of CMC information as required in an NDA (21 CFR 314.94(a)(9)(i)). The required CMC information includes, among other things, "the specifications necessary to ensure the identity, strength, quality, [and] purity... of the drug product..." (21 CFR 314.50(d)(l)(ii)(*a*) and 314.94(a)(9)).

FDA's CMC review carefully evaluates any application submitted under section 505 of the Act referencing Eloxatin injection for any oxaliplatin degradation products that may be generated during the product's labeled shelf-life. Any degradation impurities or new platinum complexes are evaluated and controlled, as specified for ANDAs in FDA's draft guidance for industry, *ANDAs: Impurities in Drug Products*[6] (ANDA impurities guidance), and as specified for NDAs in FDA's ICH[7] guidance for industry, *Q3B(R2) Impurities in New Drug Products* (ICH guidance) (both of these guidance documents are available on FDA's web site at http://www.fda.gov/cder/guidance/default.htm).

As described in the ANDA impurities guidance at 2, we recommend that applicants specify any degradation product observed during stability studies conducted at the recommended storage condition (see also ICH guidance at 2-3). FDA will examine evidence that the analytical procedures have been validated and are suitable for the detection and quantification of degradation products (ANDA impurities guidance at 2-3; ICH guidance at 3-5). FDA will ensure that analytical procedures are validated to demonstrate specificity for the specified and unspecified degradation products (Id.).

The ANDA impurities guidance and the ICH guidance describe the qualification threshold (i.e., the limit above which a degradation product/impurity must be appropriately qualified). In general, a degradant or impurity does not need to be qualified

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[6] A notice of availability for this draft guidance published in the *Federal Register* on August 29, 2005. When finalized, this guidance will represent FDA's current thinking on this topic.

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

if it occurs in a concentration below the qualification threshold. *Qualification* is the process of acquiring and evaluating data that establish the biological safety of an individual degradation product or a given degradation profile at the level or levels being considered (ICH guidance at 6; ANDA impurities guidance at 4-5). The ICH guidance spells out qualification thresholds expressed either as a percentage of the drug substance or as the total daily intake of the degradation product based on the amount of drug substance administered per day (maximum daily dose) (e.g., for a maximum daily dose between 100 milligrams (mg) to 2 grams, the qualification threshold is 0.2 percent or 3 mg total daily intake, whichever is lower) (ICH guidance at Attachment 1). Higher or lower thresholds for qualification of degradation products may be appropriate for some individual new drug products based on scientific rationale and the level of concern, including drug class effects and clinical experience (ICH guidance at 6; ANDA impurities guidance at 4-5).

If a degradation product is above the qualification threshold, it is considered qualified when certain conditions are met. A degradation product is qualified, for example, when the observed level and proposed acceptance criterion are comparable (i.e., qualified using comparative analytical studies) to the reference listed drug, when they are justified by the scientific literature, or when they do not exceed the level that has been adequately evaluated in toxicology studies (for other examples, see ICH guidance at 6, Attachment 3 and ANDA impurities guidance, section IV and Attachment 1, at 4-8).

For an aqueous oxaliplatin referencing Eloxatin injection, FDA uses appropriate CMC review to assess specific chemical information and data about whether the added conjugate base of the buffering agent replaces the oxalate ligand in the platinum complex. If new platinum complexes are generated as a result of this ligand exchange reaction, the CMC review evaluates the extent to which these new platinum complexes are generated under anticipated storage conditions. Based on these reviews, we assess whether these new platinum complexes are generated at a level below the qualification threshold, at a level requiring qualification, or at a level that would require preclinical and/or clinical studies.

If an oxaliplatin degradation product is present below the qualification threshold, or is appropriately qualified, as described in the ANDA impurities guidance and the ICH guidance, additional preclinical and/or clinical testing ordinarily would not be needed. Although we agree that it is possible that adding a buffering agent (e.g., tartaric acid) to oxaliplatin may have an impact on the safety and/or efficacy profile of the drug product, FDA will analyze the specific chemical information and stability data contained in each application to determine whether any specific degradation product requires additional preclinical and/or clinical studies to demonstrate its impact on safety or efficacy.[8]

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[8] The information and data included in your Second Supplement does not alter our analysis or conclusions. The level of any impurity in an Eloxatin product for which approval in the United States is sought (either as an ANDA or as a 505(b)(2) application) would be determined using a validated analytical method, and the standards set forth in the above-referenced ANDA impurities guidance and ICH guidance would be followed.

The Agency will not approve an application submitted under section 505 of the Act for an oxaliplatin product containing an added acid, or its conjugate base, unless, in addition to satisfying all other requirements for approval, the CMC information assures and preserves product identity, strength, quality, and purity. FDA will ensure that these formulations maintain their labeled potency throughout the product shelf-life. If new platinum complexes form as a result of the addition of an acid, or its conjugate base, these oxaliplatin degradation products will be evaluated and controlled in accordance with the recommendations provided in the ANDA impurities guidance or the ICH guidance. Therefore, FDA will ensure that the safety and effectiveness of buffered oxaliplatin would not differ from Eloxatin aqueous solution.

2. Added sugar

In the first supplement, you state that the addition of sugars to solutions of oxaliplatin raises the same concerns about by-products (i.e., degradation products, degradation impurities) as those raised by the addition of a buffer (First Supplement at 2). Accordingly, you request that the Agency require that any application for a generic version of oxaliplatin solution that contains an added sugar, citing Eloxatin as the reference listed drug, include preclinical and/or clinical studies to demonstrate safety and efficacy.

To support your argument, in addition to other literature, you submit an internal Sanofi report entitled "Stability of oxaliplatin solution in the presence of dissolved sugars" (the Report) (First Supplement, Appendix A). You state that the Report shows that the addition of sugar to an oxaliplatin aqueous solution causes increases in three types of new platinum complexes (i.e., diaquoPt(DACH), diqquoPt(DACH) dimer, and platinum (IV)[9]) in comparison to the control solution (plain aqueous solution) upon testing after 3 months in ambient (room temperature (25°C, 60 percent humidity) and accelerated conditions (40°C, 75 percent humidity) (First Supplement at 5-7). Based on these results, you argue that solutions stored at room temperature for any commercially relevant period of time (e.g., 6 months) would likely generate these complexes above 0.2 percent (First Supplement at 8, citing FDA guidance for industry, *Q1A(R2) Stability Testing of New Drug Substances and Products*). In the recently submitted Second Supplement, you reported on an effort to analyze impurities present in a generic product obtained commercially in Portugal.

Again, we agree with you that there is a possibility that an added sugar (e.g., lactose, glucose) will result in the formation of new platinum complexes, analogous to the potential for an added acid (other than oxalic acid), or its conjugate base, to result in the formation of new platinum complexes. The underlying concepts are also analogous regarding biological activity, toxicity, and the impact on safety and/or efficacy of the drug product.

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[9] You note that platinum (IV) complex represents a new impurity (First Supplement at 6). FDA would evaluate and control for any platinum (IV) complex, as described in section II.A.1 of this document, as it would any other new platinum complexes.

FDA carefully reviewed the data provided in the Report. The data show that the sugars slowed down the formation of certain platinum complexes (i.e., diaquoPt(DACH) and diquoPt(DACH) dimer) but enhanced the formation of others (i.e., platinum (IV) complex and its related unspecified degradation impurities, as well as other unspecified degradation impurities related to diaquoPt(DACH) complex) under accelerated storage conditions. When stored in ambient conditions for a limited 3 months, none of the listed impurities appear to exceed 0.2 percent and the changes in the levels appear comparable to the control group (water). While these data are useful to FDA to identify specific degradation products and their potential characteristics, the study is not complete, in depth, and/or dispositive. For example, the data provide aggregate percentages of the drug substance for each degradation impurity category, as opposed to providing the percentages for each individual degradation impurity, making it unclear whether individually, any unspecified degradation impurity could have exceeded the qualification threshold under standard long-term and/or accelerated storage conditions. Therefore, we do not believe it is appropriate to assume that similar impurities would develop in solutions stored at room temperature for any commercially relevant period of time. Although FDA considers accelerated data useful for identifying areas of potential concern, we cannot generalize a need for preclinical and/or clinical studies based on the data presented in the Report. The information and data provided with your Second Supplement does not alter our analysis.

To assess whether preclinical and/or clinical studies are necessary, FDA will conduct the CMC review for drug product formulations having an added sugar in an analogous manner to that described in section II.A.1 for buffered oxaliplatin formulations. The CMC review will evaluate any application submitted under section 505(b) of the Act referencing Eloxatin injection for any oxaliplatin degradation impurities that may be generated as a result of ligand exchange during the product's labeled shelf-life. FDA will ensure that the analytical procedures are validated and are suitable for the detection and quantification of degradation products (ICH guidance at 3-5). We will analyze specifications for the proposed drug product, the real-time stability data, and the proposed maximum daily dose. Any new platinum complex degradation product will be evaluated and controlled as specified in the ICH guidance and as discussed in more detail in section II.A.1 of this document. Accordingly, if new platinum complexes or degradation products are appropriately controlled and qualified, we believe that preclinical and/or clinical studies to demonstrate safety and efficacy will not be necessary.[10]

[10] The Agency has reviewed and is approving an application under section 505(b)(2) in which the degradation impurity levels were below the ICH qualification threshold.

III. CONCLUSION

We agree with your petition that the potential exists for oxaliplatin solutions to develop impurities if an acid (other than oxalic acid), or a conjugate base thereof, is added, or if a sugar is added. We also agree that such impurities may have an impact on the safety and/or the efficacy of the product if they occur at certain levels of concentration. We do not believe, however, that this theoretical concern requires preclinical and/or clinical testing in all instances. Instead, we intend to closely examine the degradation impurity levels for all oxaliplatin solutions and ensure that degradation impurity levels are below the threshold described in our guidance documents, or that impurities are appropriately qualified. Otherwise, for the reasons stated above, your petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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/s/

Esther Chuh
5/29/2009 09:30:18 AM
CHEMIST

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-815 Applicant Hospira Worldwide, Inc.
Drug Oxaliplatin Lyophilized Powder for Injection Strength(s)50 mg/vial and 100 mg/vial

APPROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date24 March 2009 Date_____
Chief, Reg. Support Branch Initials MHS Initials_____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days:Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☒ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter:Full Approval.
Comments:ANDA submitted on 2/9/2007(date corresponding to NCE+ped minus 1 year), BOS=Eloxatin for Injection, NDA 21492 in the D/C'd section of the OB(relisting CP 2006P-0291 filed), PIV cert to the '961, '874 and '319 patents. ANDA ack for filing with PIV on 2/9/2007(LO dated 5/21/2007). MC stamped 8/8/07-RR from Sanofi-aventis U.S. signed and dated 6/12/2007, RR from Sanofi-aventis Malvern PA signed and dated 6/11/2007, RR from Debiopharm in Hackensack NJ signed and dated 6/13/2007, CA 07-CV-03409-FLW-JJH filed in the D of NJ(Trenton) on 7/23/2007 for infringement of the '874 patent.

Since litigation commenced within 45 days of notice the stay of approval is governed by 31 CFR 314.107(b)(3)(i)(B) which is the 7.5 year stay that is calculate from the date of approval of the NDA. That said this stay is further extended by an additional 6 months due to the extension afforded by pediatric exclusivity. This fact appears solely in the statute so the approval letter will need to include language with a statutory citation(I can't provide the citation as someone stole my statute while I was on vacation). SOOO-the 8 year stay is 8/9/2002+8 years=8/9/2010. The OB has already been updated to indicate that NDA 21492 was not D/C'd for S/E reasons.

ANDA is eligible for TA only due to unexpired 8 year stay of approval.

2. Project Manager, Esther Chuh Team 2 Date 3/24/2009 Date_____
Review Support Branch Initials EC Initials_____

Original Rec'd date 2/9/2007 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 2/9/2007 Date of EER Status 10/2/2007
Patent Certification (type) IV Date of Office Bio Review 8/2/2007
Date Patent/Exclus.expires 2/9/ 2017 Date of Labeling Approv. Sum 2/17/2009
Citizens' Petition/Legal Case Yes☐ No ☒ Date of Sterility Assur. App. 2/2/2009
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☐
Priority Approval Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☐
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:

Date_____ Date_____
Name/Initials_____ Name/Initials_____

Comments:
Labeling AC in DFS 5/7/2009 by Angela Payne and John Grace - EC 5/22/2009

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 15Apr09
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:OK.

5. Div. Dir./Deputy Dir. Date5/12/09
Chemistry Div. I InitialsRMP

Comments:CMC is satisfactory for TA.

6. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date5/21/2009
Director, DLPS Initialswpr
Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☒ No ☐; Petition: Yes☐ No☒
Comments:Applicant made PIV patent certs to all listed patents; they were sued within the 45 day period on the '874 patent only; litigation ongoing; M-61 W/H exclusivity expires 7/10/2010 w/peds; no BPCA carveout done; ped info remains in proposed labeling; Labeling acceptable 5/7/2009 per TA Summary; Bio acceptable 8/2/2007; Micro acceptable 2/2/2009; EER acceptable 10/2/2007.

Okay for TA Only

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date 5/22/2009

Review Support Branch Initials EC
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:22 PM Time notified of approval by phone
3:05 PM Time approval letter faxed

FDA Notification:
5/22/2009 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/22/2009 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Esther Chuh

5/29/2009 05:26:18 PM

RECORD OF TELEPHONE CONVERSATION

DATE: **1/9/09 (Initial Contact)**

INITIATED BY: **Lisa S.G. Shelton, Review Microbiologist**

Applicant/Sponsor

Name: Hospira Worldwide, Inc. (formerly Mayne Pharma Limited)
Address: 275 N. Field Dr, D-0389, Bldg. H2-2N, Lakeforest, IL 60045-5046
Representative: Laurie Wojtko, Sr. Associate, Global Regulatory Affairs
Telephone: 224-212-6158

Clarifying question regarding:

ANDA 78-815 Oxaliplatin for Injection, Amendment dated 11/14/08

In Question 1b, we ask for the location of the lyophilizer or lyophilizers to be specified. The response states that (b) (4) [redacted].

(b) (4) [redacted]

RESPONSE:

01/09/09 I spoke with Laurie Wojtko. She said she would most likely be able to get the information on Monday or Tuesday and would get back with me.

01/12/09 Laurie called. She clarified that (b) (4) [redacted]. There was a typographical error in the response. This information will be incorporated into the review.

Drafted by L.Shelton 01/12/09
Filename V:\MICROWRK\TELECONS\78-815a1.micro.01-09-09.doc
To be filed in DFS

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

/s/

Lisa Shelton
7/23/2009 12:33:34 PM
MICROBIOLOGIST

September 3, 2009

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20855

Re: ANDA 78-815, Oxaliplatin for Injection, 50 mg/vial, 100 mg/vial

MINOR AMENDMENT – FULL APPROVAL REQUESTED

Dear Mr. Buehler,

Hospira, Inc. hereby submits a minor amendment to the above-referenced abbreviated new drug application for Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial. This is in response to the Agency's tentative approval letter dated May 22, 2009. For ease of review a copy of this May 22, 2009 correspondence is included herein.

We note and acknowledge that the reference listed drug (RLD), Eloxatin for Injection of Sanofi Synthelabo, Inc. is subject to a period of patent protection, U.S. Patent No 5,290,961 (the '961 patent), 5,338,874 (the '874 patent) and 5,420,319 (the '319 patent). We acknowledge that the above referenced ANDA was filed with a Paragraph IV certification. As the court ruled and issued a favorable summary judgment of non-infringement for the '874 patent on June 18, 2009, Hospira hereby requests final approval of this ANDA. A copy of the final judgment entered on June 30, 2009 and signed by the U.S. District Court judge has been attached and is intended to support Hospira's request for full approval.

We hereby certify that there have been no changes in the conditions under which the product was tentatively approved.

This amendment is submitted as an electronic hybrid which does not contain an XML backbone. A waiver to Memorandum 27 allowing for the acceptance of electronic submissions that are not in compliance with the guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical applications and Related Submissions Using the eCTD Specifications" was submitted on January 18, 2008 and approved on February 22, 2008. The files contained on the CD have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.5 virus scanning

Hospira Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

software. For electronic signatures a letter of non-repudiation for the undersigned (Laurie Wojtko) is on file with the FDA.

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

HOSPIRA, INC.

Laurie Wojtko 9-3-09

Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
Hospira, Inc.
Phone: (224) 212-6158
Fax: (224) 212-5401
E-mail: Laurie.Wojtko@hospira.com

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-815 Applicant Hospira Worldwide, Inc.
Drug Oxaliplatin For Injection Strength(s) 50 mg/vial and 100 mg/vial

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 9/28/2009 Date 9/30/09
Chief, Reg. Support Branch Initials swpr Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Eloxatin NDA# 21-492
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☒ No ☐ Date settled: 6/30/2009
Is applicant eligible for 180 day yes
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Approval
Comments: Comments: ANDA submitted on 2/9/2007(NCE+ped minus 1 year), BOS=Eloxatin for Injection, NDA 21-492 in the D/C'd section of the OB(relisting CP 2006P-0291 filed), applicant made PIV patent certs to the '961, '874 and '319 patents. ANDA ack for filing with PIV on 2/9/2007. Hospira was sued for infringement of the '874 patent.
Since litigation commenced within 45 days of notice the stay of approval is governed by 31 CFR 314.107(b)(3)(i)(B) which is the 7.5 year stay that is calculated from the date of approval of the NDA. This stay of approval is further extended an additional 6 months due to pediatric exclusivity. The 8 year stay (7.5 + ped) is 8/9/2002+8 years=8/9/2010. The OB has already been updated to indicate that NDA 21-492 was not D/C'd for S/E reasons. Hospira's letter dated 9/3/2009 states that the court ruled and issued a favorable summary judgement of non-infringement for the '874 patent on June 30, 2009. This ANDA is eligible for immediate approval.

2. Project Manager, Esther Chuh Team 2 Review Support Branch Date 9/29/2009 Date _____
Initials EC Initials _____

Original Rec'd date 2/9/2007
Date Acceptable for Filing 2/9/2007
Patent Certification (type) IV
Date Patent/Exclus.expires 2/9/2017
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 10/2/2007
Date of Office Bio Review 8/2/2007
Date of Labeling Approv. Sum 5/7/2009
Date of Sterility Assur. App. 2/2/2009
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date 5/22/2009
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date9/29/2009 Date9/29/2009
Name/InitialsAngela Payne Name/InitialsJohn Grace
Comments:

From: Grace, John F
Sent: Tuesday, September 29, 2009 2:20 PM
To: Payne, Angela; Chuh, Esther
Subject: RE: ANDA 78-815 Oxaliplatin FIJ/ Hospira - Request for Final AP

concur.

From: Payne, Angela
Sent: Tuesday, September 29, 2009 2:20 PM
To: Chuh, Esther; Grace, John F
Subject: RE: ANDA 78-815 Oxaliplatin FIJ/ Hospira - Request for Final AP

The labeling approval summary #3 remains acceptable. There are no new changes to the RLD in darrts, USP, or OB. The applicant submitted FPL

Angela

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 29Sep09
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:OK.

5. Div. Dir./Deputy Dir. Date9/30/09
Chemistry Div. I InitialsRMP

Comments:CMC remains satisfactory for the previously TAed application going now for AP.

6. Frank Holcombe **First Generics Only** Date 9/30/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
This ANDA was tentatively approved on 5/22/09.

7. Vacant Date_____ Deputy Dir., DLPS

Initials_____
RLD = Eloxatin for Injection, 50 mg and 100 mg/vial
Sanofi Synthelabo, Inc. NDA 21-492 (001, 002)

8. Peter Rickman Date 9/30/09
Director, DLPS Initials rlw/for

Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: This ANDa was tentatively approved on May 22, 2009. Final approval was blocked at that time by ongoing patent litigation. Refer to the administrative sign-off form completed at the time of the tentative approval.

On September 3, 2009, Hospira submitted a "minor amendment" to provide for final approval of this ANDA. Hospira referred to the final judgment entered by the court on June 30, 2009 (summary judgment of non-infringement for the '874 patent). This effectively ended the patent litigation. Hospira stated that no changes had been made in the conditions under which th eproduct was tentatively approved.

Final-printed labeling remains acceptable for approval (see above).

OR

8. Robert L. West Date 9/30/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 10/2/07 (Verified 9/30/09). No "OAI" Alerts noted.

Hospira provided paragraph IV certifications to the '961, '874, and '319 patents listed in the "Orange Book". Hospira was sued only on the '874 patent. On June 30, 2009, the court determined that the '874 patent is not infringed. This removes the legal barrier to the approval of this ANDA.

This ANDA is recommended for final approval.

9. Gary Buehler Date 9/30/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date9/30/09

Review Support Branch Initials EC
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9/30/09 Time notified of approval by phone
9/30/09 Time approval letter faxed

FDA Notification:
9/30/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
9/30/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021492 Product 001 in the OB_Disc list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021492	001	5290961	Jan 12, 2013	Y			
021492	001	5290961*PED	Jul 12, 2013				
021492	001	5338874	Apr 7, 2013	Y			
021492	001	5338874*PED	Oct 7, 2013				
021492	001	5420319	Aug 9, 2016	Y			
021492	001	5420319*PED	Feb 9, 2017				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021492	001	M-61	Jan 10, 2010
021492	001	PED	Jul 10, 2010

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

- Orange Book Data - **Monthly**
- Generic Drug Product Information & Patent Information - **Daily**
- Orange Book Data Updated Through August, 2009
- Patent and Generic Drug Product Data Last Updated: September 29, 2009

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/s/

EUNJUNG E CHUH
09/30/2009