CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202356

COMPLETE RESPONSE

Pfizer Labs
235 East 42nd Street
New York, NY 10017

Attention: Tricia Racanelli, Pharm.D.
Director, Regulatory Affairs, WRS, Emerging Markets/Established Products

Dear Dr. Racanelli:

Please refer to your New Drug Application (NDA) dated August 14, 2012, received August 14, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection Concentrate, 10 mg/mL.

We acknowledge receipt of your amendments dated August 30, October 24, and December 7 and 20, 2012.

The August 14, 2012, submission constituted a complete response to our February 29, 2012, action letter.

We also acknowledge receipt of your amendment dated January 31, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The combination of ethanol and propylene glycol in this proposed docetaxel formulation may result in an increase in the toxicity of your docetaxel product compared to that of the referenced drug (Taxotere). The magnitude of the potential increase in toxicity and the potential difference in toxicity profiles between your docetaxel product and the referenced drug remains uncertain without additional clinical information. Please provide additional information to better characterize potential alcohol-related toxicities. This information could include one of the following:

    a. Published references that enable adequate estimation of the toxicity expected from:

i. The amount of ethanol used in your product;
ii. The extent to which propylene glycol adds to ethanol intoxication; and
iii. The potential interaction between these two agents (e.g., competition for alcohol dehydrogenase).

b. Results from a clinical trial to assess the safety of your docetaxel product. A trial to assess the toxicity of ethanol and propylene glycol in combination, at amounts similar to those in your product may be acceptable if combined with adequate safety monitoring and assessment strategies for alcohol-related toxicities. The design of such a study should account for variability in expression of toxicity in patients in response to a given blood alcohol level. Should you choose to proceed with such a trial, we advise that you submit a protocol for our review

c. A reformulation of your docetaxel product to deliver ethanol and propylene glycol at amounts (individually or in combination) that are not higher than other docetaxel products.

PRODUCT QUALITY

1. Revise the composition of Docetaxel Injection Concentrate 10 mg/mL submitted on December 7, 2012, to reflect the exact amount of ethanol in %w/w or %w/v. The amount of this excipient is critical to quality and should not be approximated. In addition, provide actual representative components and compositions (per vial, not per mL) for each of the four proposed presentations. Similarly, propylene glycol and polysorbate-80 should be listed in the exact amount required for the formulation per vial (e.g., 2 mL, 8 mL, 13 mL, and 20 mL vials).

2. Revise the acceptance criteria for ethanol content to be (b) (4) % of the actual amount added in the components and composition statement (e.g., 40%v/v would be (b) (4) %v/v).

3. Include the test for alcohol content in the Post-Approval Stability Protocol and Stability Commitment and provide the stability data obtained for ethanol content.

4. Provide compatibility data for your drug product, generated using the proposed infusion line (e.g., polyethylene-lined administration) under the conditions described in the proposed package insert.

LABELING

1. We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

2. Please submit draft labeling revised as follows:

a. Throughout the labeling, please change the product name from “Docetaxel” to “Docetaxel Injection Concentrate”.

b. The current language in section 8.4 (**Pediatric Use**) of the labeling should be removed and replaced with the following statement: “The safety and effectiveness of Docetaxel Injection Concentrate in pediatric patients have not been established.”

c. In sections of the labeling where there is reference to the product’s evaluation in the clinical trial by the innovator, please replace “Docetaxel” with “docetaxel”.

3. Please submit draft carton and container labeling revised as follows:

Carton Labeling (1 count and 5 count)

a. Add the concentration per mL statement “10 mg/mL” just below the total drug content in all places that it appears. Highlight the “(10 mg/mL)” statement by placing it in a red color block background with “(10 mg/mL)” in white lettering to provide emphasis on the concentration of the product. Ensure the font size of the per mL concentration is smaller than the font size of the total drug content. Refer to the Unites States Pharmacopeia General Chapter <1> Injections for additional guidance, if needed.

b. In red color block and in white lettering add “xx mg/xx mL (10 mg/mL)” to the top of all panels of the carton labeling as a continuous banner to provide further emphasis on the concentration of the product. Additionally, delete the statement (b) (4) at the top of each carton.

c. Increase the font size of the following statements on the 1 count and 5 count cartons, respectively:

“xx mL single-use vial; discard unused portion”
“5 x xx mL single-use vials; discard unused portion”

d. With regards to the statement “Docetaxel Injection”, bold “Injection” as you did on the container labels.

Carton Labeling (5 count)

e. Increase the font size of the statements on the side panels. As currently presented, the statements are all within the top half of the side panel. Utilizing large font sizes for these statements and more of the side panel will increase readability of these statements.

Container Label and Carton Labeling for the 130 mg/13 mL Product

f. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

   i) One-vial vs. two-vial formulations
   ii) Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

   The color you propose for your 130 mg/13 mL strength is similar to the color currently utilized for a two-vial docetaxel product of a different concentration and strength. Therefore, not only could the concentrations get confused but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a different color for strength differentiation for your 130 mg/13 mL product.

Container Label and Carton Labeling for the 200 mg/20 mL Product

g. The color you propose for your 200 mg/20 mL (10 mg/mL) strength is similar to a blue color currently utilized for a different docetaxel concentration and strength. Therefore, not only could the concentrations get confused (10 mg/mL vs. 20 mg/mL) but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a different color for strength differentiation for your 200 mg/20 mL product.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/

AMNA IBRAHIM
02/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202356

COMPLETE RESPONSE

Pfizer Labs
Attention: Beatrice Curran
Associate Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Curran:

Please refer to your New Drug Application (NDA) dated April 29, 2011, received April 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection Concentrate 10mg/mL.

We acknowledge receipt of your amendments dated May 20, June 2, September 9, October 14, November 10, December 1, and December 16, 2011, and February 9, 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NONCLINICAL

1. You have not provided adequate scientific justification for the proposed levels of impurities. The proposed acceptance criteria for all identified impurities in the Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance, or to not exceed the levels detected in Taxotere. If you cannot lower the specifications as advised, you must conduct nonclinical studies to qualify these impurities, or provide sufficient data from the literature to adequately justify these proposed impurity levels.

2. You have not provided complete information regarding the levels and the safety of the leachables present in your drug product, in order for FDA to adequately evaluate their safety at the acceptance levels and expiry date proposed in your submission of December 1, 2011. Please provide this information as well as information regarding the safety of each of these leachables after intravenous administration. If you cannot qualify the safety of the levels of each of the detectable leachables from data in the literature, additional nonclinical studies will be needed.

PRODUCT QUALITY

3. Your December 1, 2011, response to question 2 of our October 7, 2011, letter, did not provide any validated analytical procedures to identify, monitor, and quantify leached components in the drug product. Propose acceptance criteria for the levels of leached compounds. Provide analytical results from batch analyses and drug product stability data to support the safety levels of [redacted] (b) (4) as identified leachables in the proposed drug product. Propose and submit acceptance criteria for the identified leachables based on provided batch analyses and stability data.

4. Provide compatibility data that adequately supports the compatibility of the drug product with the proposed syringe and infusion line (e.g., polyethylene-lined administration) under the conditions described in the proposed package insert

5. DMF [redacted] (b) (4) ([redacted] (b) (4)) is currently inadequate to support your NDA.

6. Include and propose the following tests, methods, and acceptance criteria in the drug product specification:

   a. Extractable Volume

   b. Osmolality

   c. pH

   d. Content of Ethanol

   e. Content of EDTA

7. Identify the supplier of polypropylene vials used in each of the batches submitted for batch analyses and the primary stability study.

8. Provide drug product stability data for the drug product as stored in upright and inverted positions. The vial position is not clearly specified in the stability data provided in Section 3.2.P.8.3 of your NDA. The comparison between upright and inverted positions is important to determine whether contact of the drug product with the closure results in extraction of chemical substances from the closure components or adsorption and absorption of product components into the container/closure.

9. Include tests for content of alcohol and pH in your drug product stability testing.

LABELING

We reserve comment on the proposed package insert and patient package insert until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Please submit draft carton and container labeling revised as follows:

General Comments for the Container Labels and Carton Labeling:

10. Revise the statement "Made in Australia" to "[redacted (b) (4)]."

11. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling that may help to differentiate these products is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

    - One-vial vs. two-vial formulations
    - Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

    The color you propose for your 200 mg/20 mL strength is similar to the red color currently utilized for the one-vial Taxotere 80 mg/4 mL product by Sanofi Aventis. Therefore, not only could the concentrations get confused but the strengths could get confused as well, leading to dosing errors. We request that you choose a color for strength differentiation that does not overlap with the currently marketed 80 mg/4 mL one-vial Taxotere by Sanofi Aventis.

12. Remove "Concentrate" from the established name. This could lead to confusion with the two vial concentrate preparations which have two dilution steps. Additionally, change the font color of "Docetaxel Injection" to black to make the name more prominent.

13. Revise the statement "[redacted (b) (4)]" to "For Intravenous Infusion Only" and bold the words "Infusion Only". For example: "For Intravenous **Infusion Only**".

14. Remove "[redacted (b) (4)]" because it competes with other important information and clutters the labels and labeling.

15. Change the statement “single-use” to “single-use vial”.

16. Highlight the “(10 mg/mL)” statement by placing it in a red color block background with “(10 mg/mL)” in white lettering wherever it appears on the container or carton labeling to provide emphasis on the concentration of the product.

Container Labels:

17. Place the volume, in mL, immediately in front of the statement “single-use vial” (see item #14 above). For example: “2 mL single-use vial” on the 20 mg/2 mL product and so forth.

18. Relocate the statement “Caution: Cytotoxic Agent” to the side panel of the 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL labels.

19. Ensure there is one character space between “10” and “mg/mL” in the strength presentation.

20. To highlight the difference between docetaxel products, add the following statement: “Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions.” Additionally, bold and box the statement.

21. Consider using a different orientation for the layout of the information on the principal display panel in order to accommodate the above recommended revisions to the container labels. The Sandoz and Hospira marketed docetaxel container labels are a good resource on guidance for making changes to the Pfizer product to ensure patient safety. In addition, because the container labels are small like the Hospira and Sandoz labels, you may wish to remove the statements “Store between…”, “Protect from light,…” and “Dosage and Use:…” statements by applying 21 CFR 201.10 (h)(2)(i) for minimum label requirements.

General Comments for Carton Labeling:

22. In red color block and in white lettering add “xx mg/xx mL (10 mg/mL)” to the top of all panels of the carton labeling as a continuous banner to provide further emphasis on the concentration of the product. The Sandoz and Hospira marketed docetaxel products are a good resource on guidance for this change. Do not include the “New Strength and Preparation” banner found on the Hospira and Sandoz products.

23. As a continuous banner in red color block and in white lettering add the following Statement: “Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions.”

One-Count Carton Labeling:

24. Place the volume, in mL, immediately in front of the statement "single-use vial" (see item #14 above). For example: "2 mL single-use vial" on the 20 mg/2 mL product and so forth.

Five Count Carton Labeling:

25. Remove "[redacted (b) (4)]" and combine with the statement cited in item 25 below.

26. Change the statement "[redacted (b) (4)]." to "5 x XX mL single-use vials; discard unused portion." Place the corresponding total volume where the XX is located (i.e., "5 x 2 mL single-use vials; discard unused portion" for the 20 mg/2 mL carton and so forth). This statement should be located below the NDC numbers.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
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/

PATRICIA KEEGAN
02/29/2012