

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: May 12, 2009

From: Loan Nguyen, Pharm.D, Regulatory Review Officer
CBER/OCBQ/DCM/APLB, HFM-602

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To: Darlene Hithe, RPM, OVRP/DVRPA/VVB (HFM-478)
Daryll Miller, Committee Chair, OVRP/DVRPA/CMC1 (HFM-478)
Lewis Schrage, Medical Officer, OVRP/DVRPA/CRB1 (HFM-475)

Subject: Labeling Review - Comments on product labeling (Full Prescribing
Information [FPI], container, and package labels)

Product: **Adenovirus Type 4 and Type 7 Vaccines, Live, Oral**
BLA STN: **125296/0**
Sponsor: Duramed Research Inc. (a subsidiary of Barr Pharmaceuticals
Inc.)

Background

On September 30, 2008, Duramed Research Inc. (Duramed) submitted BLA STN 125296/0 for Adenovirus Type 4 and Type 7 Vaccines, Live, Oral enteric coated tablets. Included in this original submission, Duramed submitted draft product labeling (prescribing information [PI], container, and package labels) for review. The latest version of the draft labeling was submitted on February 19, 2009.

The submitted PI is in Physicians' Labeling Rule (PLR) format.

The PDUFA action date for the submission is July 31, 2009.

The following comments and recommendations are provided to the Office of Vaccines Research and Review (OVRP) for consideration, concurrence, and conveyance, as appropriate, to the applicant. In addition, to ensure compliance to the PLR, the applicant should refer and adhere to 21 CFR 201.57 for specific requirements on content and format of the product labeling.

General Comments

Since the proposed proprietary name of the product, ---(b)(4)----, has been found unacceptable (see APLB's March 31, 2009 Review Memo), APLB refers the product as Adenovirus Type 4 and Type 7 Vaccines, Live, Oral in this review.

To enhance accessibility of information, all section and subsection headings should be consistent throughout highlights, full prescribing information (FPI) contents, and FPI sections.

A. Review of Container and Package Labels

Adenovirus Type 4 and Type 7 Vaccines, Live, Oral will be supplied as enteric coated tablets, Adenovirus Type 4 Vaccine, Live, Oral enteric coated tablet and Adenovirus Type 7 Vaccine, Live, Oral enteric coated tablet.

The product package contains two component bottles, one contains 100 tablets of Adenovirus Type 4 Vaccine and the other contains 100 tablets of Adenovirus Type 7 Vaccine.

Container (bottle) labels

- Revise the name to “Adenovirus Type 4 Vaccine, Live, Oral” for adenovirus type 4 vaccine and “Adenovirus Type 7 Vaccine, Live, Oral” for adenovirus type 7 vaccine.
- Revise “adenovirus vaccine type 7” to “adenovirus type 7 vaccine.”
- Revise “adenovirus vaccine type 4” to “adenovirus type 4 vaccine.”
- Consider revising “Do not chew” to “Do not chew or crush.”

Package (carton) labels

- Revise the name to “Adenovirus Type 4 and Type 7 Vaccines, Live, Oral.”
- Consider revising “Do not chew” to “Do not chew or crush.”
- Remove ----(b)(4)---- from the blue color block.
- Please revise the product information on the package so that an accurate description is provided and complies with 21 CFR 610.61 (g). For example, in Section 11 of the draft version of the product’s PI, it is stated that each tablet contains live adenovirus, either type 4 or type 7, at an average potency of no less than 32,000 tissue-culture infective doses.

B. Review of Prescribing Information (PI)

General

- Use command language whenever possible.
- Refrain from using the terms Phase 1, Phase 2, Phase 3 when describing a study. Consider stating the nature of the study instead.

Highlights

- The dosage form and route of administration must be on the next line underneath the product name. Consider revising “Enteric Coated Tablets” to “Enteric Coated Tablets for Oral Administration” and moving the statement to a separate line underneath the product name.
- Consider revising the DOSAGE AND ADMINISTRATION section as follows:
 - Immunization consists of one dose of two tablets, one tablet each of Adenovirus Type 4 Vaccine and Adenovirus Type 7 Vaccine.
 - Tablets should be swallowed whole. Do not chew or crush tablets to avoid releasing the live adenovirus in the upper respiratory tract.
 - Immunization should be completed at least two (2) weeks prior to potential exposure.
- Consider revising the DOSAGE FORMS AND STRENGTH section as follows:
 - Adenovirus Type 4 and Type 7 vaccine enteric coated tablets.
 - Each tablet contains live adenovirus, either type-4 or type-7, at an average potency of no less than 32,000 tissue-culture infective doses.
- Consider using command language for the CONTRAINDICATIONS section. For example,
 - Do not administer to individuals who are incapable of swallowing the entire tablet whole without chewing. Chewing a tablet could expose the upper respiratory tract to live adenovirus leading to disease.
- Please verify whether or not repeated immunization is needed for subsequent exposure. If so, please clarify if previous hypersensitivity to the vaccine is a contraindication for subsequent immunization.
- Since the virus growth is maintained in fetal bovine serum and the dried virus material includes human serum albumin, please verify if hypersensitivity to any of the ingredients is a contraindication to the use of the vaccine.
- Please assure that the subsections in the WARNINGS AND PRECAUTIONS section are listed in decreasing order of importance (i.e. relative public health significance) and reflect the information presented in the FPI. (See comment for WARNINGS AND PRECAUTIONS section in FPI below).
- Please verify if Adenovirus Type 4 and Type 7 Vaccines, Live, Oral is a Pregnancy Category D product, which is defined as a product that has positive human risks findings. These findings must be presented as a warning in the WARNINGS AND PRECAUTIONS section and if a pregnancy registry exists, please state “Pregnancy registry available.”

- If Adenovirus Type 4 and Type 7 Vaccines, Live, Oral is a Pregnancy Category D vaccine and a pregnancy registry exists, please add the statement “Pregnancy registry available” to the USE IN SPECIFIC POPULATIONS section.
- Revision date will be the month/year that BLA is approved. If the submission is approved on its PDUFA action date, then the revision date will read “Revised: July 2009” or “Revised: 7/2009.”

Full Prescribing Information: Contents

- The section and subsection headings should match the section and subsection headings used in the FPI.
- Delete the periods after the numbers for the section and subsection headings.

Full Prescribing Information (FPI)

- Delete the periods after the numbers for the section and subsection headings.

Indications and Usage

- Revise the information so that it is consistent with the INDICATIONS AND USAGE section in Highlights section.

Dosage and Administration

- Please verify if the tablets can be taken with or without food (i.e., on an empty stomach or not).
- Minor revisions may be needed to improve readability. For example,
 - Adenovirus Type 4 and Type 7 Vaccines, Live, Oral is to be administered orally as one dose of two tablets, one tablet each of Adenovirus Type 4 Vaccine and Adenovirus Type 7 Vaccine [either with or without food]
 - Tablets should be swallowed whole without chewing or crushing.
 - Immunization should be completed at least two (2) weeks prior to potential exposure.

Dosage Forms and Strengths

- Please include the description of identifying characteristics of dosage forms (i.e., imprinting, scoring, shape, color and coating).
- For example:
 - Adenovirus Type 4 Vaccine tablet
White to off-white, round with no score, enteric coated tablet, imprinted with stylized b on one side.

- Adenovirus Type 7 Vaccine tablet
Light peach, round with no score, enteric coated tablet, imprinted with stylized b on one side.

Contraindications

- Consider revising the information as recommended above in the Highlights section.

Warnings and Precautions

- Items in this section should be listed in order of importance. Note that the Warnings and Precautions subsection of the Highlights section should reflect the order in this section.

Adverse Reactions

- We recommend a description of the overall adverse reaction profile of the product based on the entire safety database be presented at the beginning of this section. There is no subsection header for this description.
- Please verify whether or not there is any serious adverse reaction associated with the use of the vaccine. If there is serious adverse reactions, a brief summary of the most clinically significant information should be presented in the overall adverse reaction profile.
- Subsection 6.1 is reserved for “Clinical Trials Experience.” It is followed by the statement:

“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 clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- Please revise “Phase 3 Study” to “Clinical Trials Experience.”
- Please verify whether or not there is post marketing experience associated with the precedent adenovirus vaccine formulation (i.e., Wyeth formulation).

Use in Specific Populations

- 8.1 Pregnancy: please revise the information so it is consistent with the information presented in the highlights and consider including a description of any available human or animal reproductive and development toxicity data.

Description

- Please delete “unique” because it might be promotional.

Patient Counseling Information

- Subheadings are not necessary in this section.

- Consider presenting the information in a bulleted list focused on advising the physician on discussion points to address with the patient.
- Do not place the revision date at the end of the FPI since it already appears at the end of the Highlights section.

Conclusion

The above comments and recommendations have been provided from a comprehension and promotional perspective to assist you in revising the proposed labeling materials. If you have any questions with regards to this review please contact Loan Nguyen, Pharm.D, Regulatory Review Officer at 301-827-6333.

Firm: Duramed

Document type: Review Memorandum

Bcc: HFM-602 L. Nguyen
HFM-602 APLB Chronologic File
HFM-602 APLB Historical File

History:

Prepared: L. Nguyen 5/4/09
Commented: L. Stockbridge 5/7/09, 5/11/09
Commented: E. Ibarra-Pratt 5/12/09
Final: L. Nguyen 5/12/09

Filename: LR_AdenovirusVaccine_125296_PIVialCarton_12May09.doc

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