Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch

REVIEW MEMORANDUM

Date: January 29, 2009

To: Anissa Cheung, Committee Chair, OVRR/DVP/HFM-445
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Subject: **BLA 125297** Agrippal (Influenza Virus Vaccine)
Comments on draft product labeling

This review concerns draft labeling for Agrippal (Influenza Virus Vaccine) that was submitted to the Agency in June 2008. The original submission included draft prescribing information (PI), carton, bulk carton, and container labels. The Advertising and Promotional Labeling Branch (APLB) has reviewed the draft labeling that accompanied the original submission and has the following comments and recommendations:

Comments

PI – General Comments

- The product registration symbol should not appear in the Highlights section and may only appear once, at first use of the product name, in the Full Prescribing Information.
- Use command language throughout the PI.
- Avoid the use of periods between the section number and section header
- For clarity, refrain from the use of the following terms when describing clinical study data: pivotal, primary (or co-primary) endpoint

PI – Highlights Section

- The information in the Highlights section should be limited to a half page.
- The Highlights limitation statement is required to be bolded and must be verbatim

> **These highlights do not include all the information needed to use Agrippal (Influenza Virus Vaccine) safely and effectively. See full prescribing information for Agrippal.**

- Simplify the dosage form following the proper name for Agrippal as follows

Agrippal (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
20xx-20xx Formula

- The DOSAGE AND ADMINISTRATION subsection of the Highlights should only include the recommended dosing regimen. The dosage form and strength information belong in the subsequent subsection. The fact that Agrippal is supplied in single-dose pre-filled glass syringes belongs in the HOW SUPPLIED section of the Full Prescribing Information, not in the Highlights section. Therefore, we recommend that this section simply state

  Single 0.5 mL intramuscular injection.

- The DOSAGE FORMS and STRENGTHS subsection of the Highlights should not include description or "How Supplied" information. Thus, we suggest that you delete the second bullet that Agrippal "does not contain thimerosal or any other preservative."

- For class consistency and to avoid the misleading implication that there are adequate and well-controlled clinical trials or substantial clinical experience demonstrating that there is no detrimental effect (in efficacy or safety) when Agrippal is given at the same time as other vaccines, consider limiting the DRUG INTERACTIONS subsection bullets to those used in the Highlights for the rest of the influenza vaccine product class (i.e., remove the first bullet "Agrippal may be given at the same time as other vaccines").

- With the exception of use in pregnancy, the absence of information about the safety or efficacy of Agrippal in a specific population should not be included in the Highlights subsection USE IN SPECIFIC POPULATIONS. Thus, the statement regarding the safety and effectiveness in children (an indication that has not been established) should not be included in this subsection of the Highlights. Similarly, the statement regarding safety and effectiveness in adults, aged 18-60, considered at risk for severe influenza disease (i.e., those with chronic circulatory conditions, respiratory conditions, or diabetes) should not be included in this subsection. While not expressly stated in the draft PI (this must be amended as described below), Agrippal appears to be a Pregnancy Category B product. Therefore, the USE IN SPECIFIC POPULATIONS subsection of the Highlights should state

  Pregnancy: Reproduction studies have been performed in rabbits at doses up to 15 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Agrippal. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (8.1)

  Geriatrics: Antibody responses were lower in the geriatric population than in younger adults. (8.5)

PI – Full Prescribing Information (FPI)

- To be consistent with the INDICATIONS AND USAGE sections of the FPI across the class of influenza vaccines, we suggest that the following qualifier be added to this section

  > This indication is based on immune response elicited by Agrippal. There have been no controlled efficacy trials demonstrating a decrease in influenza disease after vaccination with Agrippal [See Clinical Studies (14)].

- The DOSAGE AND ADMINISTRATION section may be simplified to accentuate the most important information necessary for safe use of Agrippal. For example

  > **2 DOSAGE AND ADMINISTRATION**
  > **For intramuscular administration only.**
  >
  > **2.1 Preparation for Administration**
  > Shake the contents of each Agrippal vaccine syringe and inspect visually for particulate matter or discoloration. If either condition exists, do not administer the contents of the syringe.
  >
  > Do not use vaccine that has been frozen.
  >
  > **2.2 Recommended Dose and Schedule**
  > Administer Agrippal as a single 0.5 mL injection into the deltoid muscle of the upper arm. Avoid injection into the gluteal region or other areas where there may be a major nerve trunk.

- The DOSAGE FORMS AND STRENGTHS section should not contain “How Supplied” information. Consider the following for this section

  > **3 DOSAGE FORMS AND STRENGTHS**
  > Agrippal is a sterile aqueous suspension for intramuscular injection. Each 0.5 mL dose contains 15 micrograms hemagglutinin from each of 3 influenza virus strains in the vaccine for a total of 45 micrograms. [See DESCRIPTION (11)]

- The DOSAGE FORMS AND STRENGTHS section should not contain information about preservatives. This information belongs in the DESCRIPTION section.

- In section **6 ADVERSE REACTIONS** the overall adverse reaction profile from the entire safety database (pooled adverse reaction data) must be presented directly beneath the section header. Adverse reactions should be listed by body system, severity, decreasing frequency or a combination of these.

- Exhaustive lists of less common adverse reactions should be avoided in the Clinical Trials Experience subsection of the ADVERSE REACTIONS section. For Table 2, consider grouping the adverse reactions by body system and removing adverse reactions that occurred at a frequency of less than 2% (or some other cut-off frequency). The accompanying text should be revised to be consistent with the decisions made for Table 2.

- In the Clinical Trials Experience subsection of the ADVERSE REACTIONS section, the separate heading for the child and adolescent demographic of Study 1 is misleading because it implies that there is substantial clinical experience with the use of Agrippal in this demographic when, in fact, Agrippal is not approved for use in individuals less than 18 years of age. To avoid implication of approval for use in this demographic, data insufficient to warrant a pediatric indication should appear only in the Pediatric subsection of the USE IN SPECIFIC POPULATIONS section of the FPI. Furthermore, the sentence "Agrippal was generally well tolerated in these age groups and consistent with that reported for healthy adults" should be deleted.

- In the Clinical Trials Experience subsection of the ADVERSE REACTIONS section, the sub-subsection entitled "Adults at Risk" is misleading because it implies that there is substantial clinical experience with the use of Agrippal for these specific conditions when, in fact, Agrippal has not been adequately studied for use in adults with particular risks. Thus, we suggest that this sub-subsection be deleted.

- In the Postmarketing Experience subsection of the ADVERSE REACTIONS section, the inclusion of detailed descriptions of unapproved uses for Agrippal is misleading because it implies that there is substantial clinical experience outside of the demographic for which Agrippal is indicated. We recommend that the first two paragraphs of the Postmarketing Experience subsection should be deleted.

- For the DRUG INTERACTIONS section, are there data (efficacy or safety) supporting the concomitant administration of Agrippal with other vaccines. If there are no data, the first subsection should be revised (i.e., How do we know that there is no decreased efficacy with concomitant immunization or that the adverse reactions may be intensified?) and a statement added to say that there are no data.

- Based on the description of clinical data in pregnancy, presented in the Pregnancy subsection of 8 USE IN SPECIFIC POPULATIONS, Agrippal appears to be a Category B product. This subsection must identify the pregnancy category. For Category B products, the regulations require the following language

  > Pregnancy Category B. Reproduction studies have been performed in rabbits at doses up to 15 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Agrippal There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human

> response, this drug should be used during pregnancy only if clearly needed.

We recommend that the current wording in this subsection be deleted and replaced with the required language. A description of the rabbit study should be included following the required wording. Remove CDC advice and any other references that do not apply to clinical studies with Agrippal.

- Subsection 8.2 is "Labor and Delivery," not "Lactation." This is not a necessary section for an influenza vaccine.

- Subsection 8.3 is "Nursing Mothers," not "Lactation." Because there are no data demonstrating the effect of Agrippal on human milk, we suggest that you revise the subsection to simply state that this information is not known. For example

> It is not known whether Agrippal is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Agrippal is administered to a nursing woman.

- If there are no data establishing the safety and efficacy of Agrippal use in pediatric subjects, this section should be revised to be clear that there is a lack of data to warrant approval for the use of Agrippal in this population. The statement "Clinical data are available in 802 pediatrics subjects..." in the absence of qualification as to why this is not substantial evidence, misleadingly implies that there are data supporting this as an indication. If there is no pediatric indication for Agrippal, we suggest that this subsection first state that safety and effectiveness have not been established and clearly indicate that these data are from adverse reactions reported for 802 children. For example

> The safety and effectiveness of Agrippal for pediatric patients has not been established.
>
> Adverse reactions reported in 802 pediatric subjects (3 to 17 years of age) evaluated during clinical trials for Agrippal were similar to that reported for healthy adults.

- Inclusion of Subsection 8.6 Adults at Risk implies that there is sufficient data available concerning the use of Agrippal in this demographic. Since the safety and effectiveness of Agrippal has not been established in this demographic, we commend that this subsection be deleted.

- Studies that imply effectiveness for an unapproved use should be excluded from the CLINICAL STUDIES section of the PI. Thus, subsection 14.3 should be deleted.

- Outdated references should be deleted from the REFERENCES section of the PI. Consider deleting the first ACIP reference that appears to be superseded by the fourth ACIP reference.

- The reference list appears to be numbered as though each reference is a section onto itself. Please revise. Also, please ensure that the references listed are cited in the text of the PI.

- The HOW SUPPLIED/STORAGE AND HANDLING section should include strength and potency information as well as storage and handling information. Information on administration (e.g. "Immunization should be carried out by intramuscular injection") is redundant to the DOSAGE AND ADMINISTRATION section of the PI and should be deleted from the HOW SUPPLIED/STORAGE AND HANDLING section. Similarly, the statement regarding potential anaphylaxis following the administration of Agrippal does not belong in this section.

- Revise the PATIENT COUNSELING INFORMATION section to command language.

Carton and Container Labels

APLB recommends that the statement regarding lack of preservatives, including lack of thimerosal, be deleted from the carton labels.

The above comments are provided from a comprehension and an advertising and promotional labeling perspective to assist you in revising the proposed labeling materials. If you have any questions, please contact Lisa Stockbridge at 301-827-6226.

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