MedImmune

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August 24, 2009

Donald Dutra
Military Vaccine (MILVAX) Agency
5113 Leesburg Pike
Ste 402
Falls Church, VA 22041

Dear Donald Dutra:

Thank you for your recent inquiry concerning the use of FluMist®.

Attached are individual answers and a bibliography for each of the questions you asked. These are itemized below:

- **Flumist® (Influenza Vaccine Live, Intranasal) and self-administration [CAIVKI845]**

Your interest in FluMist® is appreciated. This letter and citations are not intended to offer an opinion or advice on administering our products in a manner inconsistent with product labeling. A copy of the currently approved U.S. package insert(s) and designated (*) literature reprints are enclosed for your review. Please feel free to call us if we can be of further assistance.

Sincerely,

Eddie Carver

Eddie Carver, PharmD
Senior Information Specialist

GENERAL PRODUCT INFORMATION: FluMist® is a live trivalent nasally-administered influenza vaccine with several characteristics that differ from injectable trivalent inactivated influenza vaccine (**TIV**). The three influenza strains contained in FluMist are *cold-adapted* in that they replicate efficiently at low temperatures such as 25°C, are *temperature-sensitive* in that their replication is reduced at higher temperatures of 37°C (for influenza B) and 39°C (for influenza A), and are *attenuated* in that they do not produce classical influenza-like illness in the ferret model of human influenza infection (*package insert*). FluMist and its earlier prototype formulations are commonly referred to by the CDC (Center for Disease Control & Prevention) as Live Attenuated Influenza Vaccine (**LAIV**).

Like all US influenza vaccines (injection or intranasal), FluMist contains the antigenically-related CDC recommended strains (bold text) for the 2009-10 vaccine: *A/South Dakota/6/2007(H1N1)* **[A/Brisbane/59/2007 (H1N1)-like]**, *A/Uruguay/716/2007(H3N2)* **[A/Brisbane/10/2007 (H3N2)-like]**, and ***B/Brisbane/60/2008***. The B strain is changed from the 2008-09 seasonal vaccine (*CDC-ACIP 2009*). The influenza vaccine composition in the 2009-010 influenza season is identical to that recommended by the World Health Organization in February 2009 for the Northern Hemisphere's 2009-10 influenza season. For people traveling to the Southern hemisphere, it should be noted that **A/Brisbane/10/2007 (H3N2-like)** and **A/Brisbane/59/2007** are current Southern Hemisphere vaccine virus strains as well.

FluMist is indicated for the active immunization of children and adults, 2-49 years of age (*package insert*). The relative efficacy of FluMist in preventing culture-confirmed influenza in a multinational, randomized, double-blind, active-controlled (inactivated influenza vaccine, aka "flu shot") study in healthy children <5 years old at enrollment was 44.5% (*package insert*). In a multi-center, randomized, double-blind, placebo-controlled study in healthy adults, the protection afforded by FluMist against a challenge of a single strain of wild-type influenza virus was 85% (*Treanor 2000*). Vaccination with FluMist has been demonstrated to induce both serum (IgG) and nasal secretory (IgA) antibodies (*Belshe 2000, Boyce 2000, Treanor 2000).*

FluMist has been extensively studied in people 6 weeks to 98 years of age and has a well documented safety & efficacy profile. The most common adverse reactions are runny nose or nasal congestion in all ages, fever >100°F in children 2-6 years of age, and sore throat in adults. See the enclosed prescribing information for a complete description of the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS for FluMist. Recommendations of the **CDC Advisory Committee on Immunization Practice**s (CDC-ACIP) for the prevention and control of influenza were last published July 24, 2009 (*CDC-ACIP 2009*). Recommendations from the American Academy of Pediatrics concerning flu immunization of children were updated in July 2009 (*AAP 2009*). Each pre-filled FluMist sprayer must be stored at 2-8° C (35-46°F) and carefully monitored for its expiry date. **FOR NASAL ADMINISTRATION ONLY. DO NOT ADMINISTER PARENTERALLY. (Note – an updated package insert for FluMist and the latest approved vaccine formulation is made available in the summertime prior to each new influenza season.)**

RE: FluMist® (Influenza Vaccine Live, Intranasal) and self-administration *[CAIVKI845]*

FluMist® should be administered by a healthcare practitioner and the pictorial panels in the package insert are based on such use. As further noted in the FluMist package insert under DOSAGE AND ADMINISTRATION,

> "*Once FluMist has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container.*"

The FluMist package insert also states that:

> *"Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine."*

FluMist should only be administered by a healthcare provider. There are limited data on self-administration of the product in adults; there is no data for children less than 18 years of age. In a study of 4,561 healthy working adults 18-64 years of age, participants were provided with instructions on intranasal administration of the vaccine and were given the option of either self-administration under direct supervision of a trained study staff member or administration by a

study staff member *(Nichol 1999)*. Seventy-one percent of FluMist recipients and 69% of placebo recipients self-administered the dose. In both groups, 96% of persons self-administering did so without difficulty. A separate analysis of these data suggested that efficacy outcomes were better when FluMist was administered by a healthcare practitioner (*Data on file*). However, when the analysis was controlled for several confounding variables, the differences were not significant. Since the study was not designed to robustly compare effectiveness outcomes by administration method, it is difficult to draw conclusions in this regard.

In a subsequent study by the Louisville, Kentucky Department of Health, self-vaccination with FluMist was assessed in two 4-hour community walk-in immunization clinics (*Zahn 2009*). The first event was for community first-responders (i.e., police, fire, EMS) and the second event was open to general members of the community. The events were staffed by one nurse, one physician and 10 ancillary staff. A total of 224 people were immunized in the two 4-hour events. Individuals were immunized in groups of 1-25 individuals, with a maximum of 49 individuals immunized in 1 hour. Two patients were not able to self-vaccine; 1 person with an anxiety disorder and 1 person with a mild neuromuscular disorder. Side-effects were reported in 2.7% of vaccinees, but no serious side-effects were occurred. Of those individuals that self-administered the vaccine, 96% reported that they felt they used the vaccine correctly, and 96% stated that they would like to self-administer the vaccine in the future.

LITERATURE CITED: (reprints enclosed as marked below with an * - no reprints attached for FAX or e-m)

*FluMist® (Influenza Vaccine Live, Intranasal). 2009-2010 Formulation. MedImmune, LLC. Product/prescribing information as of June 2009. [MRM45636]

*AAP (American Academy of Pediatrics). Policy Statement. Prevention of influenza: Recommendations for influenza immunization of children, 2009-2010. *Pediatrics* 2009;123:1-29 Early Release [MRM45596]

*Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted intranasal influenza virus vaccine. *J Infect Dis*. 2000;181:1133-1137. [MRM 19,176]

*Boyce TG, Gruber WC, Coleman-Dockery SD, et al. Mucosal immune response to trivalent live attenuated intranasal influenza vaccine in children. *Vaccine*. 2000;18:82-88. [MRM 19,385]

*CDC-ACIP (Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices). Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP).*MMWR* 2009/July 31;58 (RR-8):1-52 [MRM45649]

*Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults. *JAMA*. 1999;282:137-144. [MRM 19,177]

*Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. *Vaccine*. 2000;18(9-10):899-906. [MRM 19,170]

Zahn MM, Carrico R. Mass vaccination by self-vaccination with live attenuated influenza. Presented at the 43rd National Immunization Conference, Dallas, TX. April 1, 2009. [MRM42855] [MRM45776]