

Medicare Chief Vows Health System 'Redesign'

BY KEITH HAGLUND

Dr. Donald Berwick, in his first major speech as administrator of the Centers for Medicare and Medicaid Services, said that he intends to change the U.S. health care system profoundly and do it by aggressively implementing the Affordable Care Act.

The job "I came here to do is helping to change health care in America to re-

alize its full potential," Dr. Berwick said during the speech to health insurance executives at the America's Health Insurance Plans' 2010 Medicare Conference.

Dr. Berwick asked the executives for their help in taking the Affordable Care Act beyond its current modest beginnings.

"We need your help. Our nation needs your help. You have and will have a profound influence on the direction our

country will take in the crucial next few years," Dr. Berwick said at the conference.

Calling the new act primarily "a question" rather than an answer, Dr. Berwick said it asks, "Will we redesign health care in America?"

In a more sobering note, the CMS chief also said that "those who wish only to preserve the status quo ... cannot be effective partners, and we simply

do not have time to pretend that they are. We do not have time for games anymore."

Dr. Berwick, the former president and CEO of the Institute for Healthcare Improvement, said he would guide the CMS by the "triple aim" set of goals he established at IHI: better quality of care for patients through efficiency and "patient centeredness," better health for populations through illness prevention, and lower costs by cutting waste and medical errors. "I intend to guide CMS toward the Triple Aim as our highest-level goal," he said.

'Those who wish only to preserve the status quo ... cannot be effective partners, and we simply do not have time to pretend that they are. We do not have time for games anymore.'

Dr. Berwick said that too much U.S. health care is now fragmented, and explained in personal terms what he meant.

"Too many of us know what fragmented, disorganized care looks like. You have to tell your name and address and story again and again to everyone you see. No one seems to talk to each other. Your record is forgotten or unavailable. One doctor prescribes a medicine that conflicts with a medicine another doctor prescribed," he said.

President Obama appointed Dr. Berwick to lead CMS on July 7 during a congressional recess, bypassing what looked to be a lengthy fight in the Senate for the nominee's confirmation. On the day Dr. Berwick spoke at the AHIP conference, however, the president re-submitted his nomination for full appointment - which would require Senate hearings and a vote - for the second time.

In August, Senate Republicans refused to accept the president's first resubmitted nomination, citing the body's brief periods in session. ■

Fluzone® High-Dose Influenza Virus Vaccine 2010-2011 Formula

R_x only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE

Fluzone High-Dose is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

DOSAGE AND ADMINISTRATION

Dosage and Schedule
Basic dosing information for Fluzone High-Dose, and its respective age indication, is presented in Table 1.

Table 1: Fluzone High-Dose

Any vaccination status	Dose/Route	Schedule
65 years and older	0.5 mL/ Intramuscular	1 dose

Administration

Inspect Fluzone High-Dose syringes visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered. Shake the syringe before administering the vaccine. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to the Advisory Committee on Immunization Practices (ACIP) recommendations.¹ If Fluzone High-Dose is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at separate injection sites.

Adults 65 years of age and older

Fluzone High-Dose should be administered as a single intramuscular dose preferably in the deltoid muscle.

DOSAGE FORMS AND STRENGTHS

Fluzone High-Dose
Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, for adults 65 years of age and older, distinguished by a gray syringe plunger rod. Each 0.5 mL dose of Fluzone High-Dose contains influenza split virus antigens that are formulated to contain a total of 180 mcg of influenza virus hemagglutinin, 60 mcg each from the 3 influenza virus strains in the vaccine.

CONTRAINDICATIONS

Do not administer Fluzone High-Dose to anyone with a known hypersensitivity to egg proteins or any component of the vaccine, or life-threatening reactions after previous administration of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone High-Dose should be based on careful consideration of the potential benefits and risks.

Altered Immunocompetence

If Fluzone High-Dose is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone High-Dose may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Fluzone High-Dose

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, active-controlled, double-blind trial conducted in the US. The safety analysis set included 2,573 Fluzone High-Dose recipients and 1,260 Fluzone recipients.

Table 2 summarizes solicited injection site and systemic adverse events collected within 7 days post vaccination via diary cards. Onset was usually within the first 3 days after vaccination and majority of the reactions resolved within 3 days.

Table 2: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

^aN is the number of subjects in the Safety Analysis Set.

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to standard Fluzone in adults 65 years of age and older.

Table 3 summarizes the severity of solicited adverse events that occurred during the first week after vaccination².

Table 3: Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection Site Pain		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
Injection Site Erythema		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
Injection Site Swelling		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
Myalgia		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
Malaise		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
Headache		
Mild	12.6	11.7
Moderate	3.1	2.5
Severe	1.1	0.3

Table 3 (continued): Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Fever		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

^aN is the number of subjects in the Safety Analysis Set.

The rates of Serious Adverse Events (SAEs) were comparable between the two groups: 156/2573 (6.1%) of Fluzone High-Dose recipients and 93/1260 (7.4%) of Fluzone recipients experienced SAEs. No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the follow-up period of the study: 16/2573 (0.6%) among Fluzone High-Dose recipients and 7/1260 (0.6%) among Fluzone recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases.

Post-Marketing Experience

The following events have been reported during the post-approval use of Fluzone. Because these events 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 vaccine exposure.

- **Blood and Lymphatic System Disorders:** Thrombocytopenia, lymphadenopathy
- **Immune System Disorders:** Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- **Nervous System Disorders:** Guillain-Barré syndrome (GBS), convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- **Vascular Disorders:** Vasculitis, vasodilatation/flushing
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, pharyngitis, rhinitis
- **Skin and Subcutaneous Tissue Disorders:** Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions:** Pruritus, asthenia/fatigue, pain in extremities, chest pain

Other Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of Fluzone and other influenza vaccines. Although Fluzone and Fluzone High-Dose contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have egg allergy. Allergic reactions include anaphylaxis, angioedema, hives, and asthma.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

USE IN SPECIFIC POPULATIONS

Fluzone High-Dose

Pediatric Use: Safety and effectiveness of Fluzone High-Dose in children have not been established.

Geriatric Use: Fluzone High-Dose is indicated for adults 65 years of age and older.

CLINICAL STUDIES

Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, randomized, active-controlled, double blind trial conducted in the US. Of those, 3,851 (2,576 randomized to Fluzone High-Dose and 1,275 randomized to Fluzone) were included in the immunogenicity analysis according to the vaccine they were randomized to receive.²

The primary endpoint of the study was HI titer 28 days after vaccination. Pre-specified statistical superiority criteria required that (1) the lower limit (LL) of the 2-sided 95% CI of the GMT ratio [Fluzone High-Dose/Fluzone] be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that (2) the lower limit of the 2-sided 95% CI of the seroconversion rate difference [Fluzone High-Dose - Fluzone] be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>-10%). As shown in Table 4, statistically superior HI titers after vaccination with Fluzone High-Dose compared to standard dose Fluzone were demonstrated for two of the three influenza strains. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to standard dose Fluzone in individuals 65 years of age and older.

Table 4: GMT Ratios and Seroconversion Rates Following Vaccination with Fluzone High-Dose

Influenza Strain	GMT		GMT Ratio	Seroconversion % ^a		Difference [Fluzone High-Dose minus Fluzone (95% CI)]	Met Both Pre-defined Endpoints? ^b
	Fluzone High-Dose N=2576	Fluzone N=1275		Fluzone High-Dose N=2576	Fluzone N=1275		
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

Note: As defined in the study protocol:

^aSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a 4-fold increase for those with pre-vaccination titer ≥1:10.

^bN is the number of subjects in the Immunogenicity Analysis Set.

^cPredefined superiority endpoint for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose minus Fluzone) is >10%. Predefined superiority endpoint for GMT ratio: the lower limit of the 95% CI for GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5.

REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR-8):1-52.
- NCT00391053; www.clinicaltrials.gov

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex.

Fluzone High-Dose

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton - NDC 49281-385-65.

Storage and Handling

Store Fluzone High-Dose refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone High-Dose contains killed viruses and cannot cause influenza. Fluzone High-Dose does not prevent other respiratory infections.

- Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their health care provider and/or to VAERS.

Fluzone is a registered trademark of Sanofi Pasteur Inc.

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