

# OA Patients at Substantial Cardiovascular Risk

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FROM THE ANNUAL EUROPEAN CONGRESS OF  
RHEUMATOLOGY

ROME — Cardiovascular risk profiles in osteoarthritis patients are, on average, comparable with those in patients with rheumatoid arthritis, according to a Dutch study.

In recent years, much attention has been focused on the elevated risk of

cardiovascular events in patients with rheumatoid arthritis, as a consequence of their increased prevalence of the standard cardiovascular risk factors coupled with a further boost in risk resulting from the chronic systemic inflammatory disease process.

By comparison, the cardiovascular risk associated with osteoarthritis has received far less attention, Dr. Inger Meek observed.

She determined the cardiovascular risk profiles of 285 consecutive rheumatoid arthritis patients and 112 consecutive osteoarthritis patients using the SCORE (Systematic Coronary Risk Evaluation) system, which is routinely employed in European clinical practice in lieu of the Framingham risk score.

The two study populations were similar in terms of mean age and sex.

The mean disease duration of the

rheumatoid arthritis patients was 6.8 years.

In all, 18% of the osteoarthritis patients in the study had a greater-than-10% estimated 10-year risk of a fatal cardiovascular event by SCORE, as did 15% of rheumatoid arthritis patients, according to Dr. Meek of the University of Twente in Enschede, the Netherlands.

Hypercholesterolemia was significantly more prevalent in the osteoarthritis patients, by a margin of 45%, compared with 29% for rheumatoid arthritis patients. The two groups did not differ significantly in terms of the other elements of SCORE (smoking status, systolic blood pressure, age, and sex).

The SCORE system, developed by the European Society of Cardiology, is based upon 3 million person-years of observation, and doesn't factor in body mass index, Dr. Meek noted.

Obesity is a well-established cardiovascular risk factor, and its prevalence is greatly increased in patients with osteoarthritis. Thus, SCORE likely underestimates their true cardiovascular

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mortality risk.

Recent evidence-based recommendations by the European League Against Rheumatism advise physicians to apply a 1.5 multiplication factor to the conventional cardiovascular mortality risk SCORE in rheumatoid arthritis patients who meet two of three criteria: disease duration greater than 10 years, rheumatoid factor or anti-cyclic citrullinated peptide positivity, or extra-articular disease manifestations (Ann. Rheum. Dis. 2010;69:325-31).

This recommendations is designed to account for the heightened cardiovascular risk imposed by a high degree of systemic inflammation.

The substantial percentage of osteoarthritis patients in this investigation with a greater-than-10% estimated likelihood of cardiovascular death within 10 years is of particular concern, Dr. Meek stressed, because the prevalence of osteoarthritis is expected to mushroom in the near future as a result of the graying of the baby boom generation.

Dr. Johannes W.J. Bijlsma of the University Medical Center Utrecht (the Netherlands) commented that the take-home message of Dr. Meek's study is that physicians need to be aware that it's not only their rheumatoid arthritis patients but also their osteoarthritis patients who are at increased cardiovascular risk. ■

**Disclosures:** Dr. Meek declared having no financial conflicts.

## Fluzone<sup>®</sup> High-Dose Influenza Virus Vaccine 2010-2011 Formula

R<sub>x</sub> 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.<sup>1</sup> 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 pre-filled 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 pre-filled 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
<b>Injection site reactions</b>		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
<b>Systemic adverse events</b>		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

\*N 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 vaccination.\*

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
<b>Injection Site Pain</b>		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
<b>Injection Site Erythema</b>		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
<b>Injection Site Swelling</b>		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
<b>Myalgia</b>		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
<b>Malaise</b>		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
<b>Headache</b>		
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
<b>Fever</b>		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

\*N 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, vasodilation/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.<sup>2</sup>

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 % <sup>3</sup>		Difference	Met Both Pre-defined Endpoints? <sup>2</sup>
	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:

<sup>1</sup>Seroconversion: 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.

<sup>2</sup>N is the number of subjects in the immunogenicity analysis set.

<sup>3</sup>Predefined 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. 2. NCT00391053; www.clinicaltrials.gov.

### HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

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

#### Fluzone High-Dose

Pre-filled syringe, without needle, 0.5 mL, package of 10 pre-filled 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.

Manufactured by:  
Sanofi Pasteur Inc.  
Swiftwater PA 18370 USA

MKT20500-2

Product information  
as of July 2010.

Printed in USA

5959-60-61