

# TZD May Boost Fracture Risk for Men, Women

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FROM THE ANNUAL SCIENTIFIC SESSIONS OF  
THE AMERICAN DIABETES ASSOCIATION

ORLANDO — Hip and distal fractures were found to be elevated both in women and men who had taken thiazolidinediones in an analysis of all hospitalizations for fracture in Scotland during 2000-2008.

The current product labels for rosigli-

tazone and pioglitazone state that the fracture risk associated with the thiazolidinedione (TZD) class is predominantly for distal fractures in women. But the current study, which included an analysis using patients as their own controls to overcome treatment allocation bias, showed that the risk of hip fractures is substantially elevated in men and women. The findings suggest that the Food and Drug Administration should

consider whether a change in drug label is indicated, Dr. Helen Colhoun, professor of public health at the University of Dundee, Scotland, said at the meeting. No difference in risk was noted between the two individual TZDs, she noted.

A clinical database identified all individuals in Scotland aged at least 40 with diagnosed type 2 diabetes, and linked those data with hospital admission records. The study comprised a total

82,027 person-years of TZD use in 35,606 users (68% rosiglitazone, 32% pioglitazone) and 6,209 fractures in 5,094 individuals.

There were 1,375 fractures among the 35,606 with diabetes who had used TZDs (3.9%) and 4,835 among the 112,100 (4.3%) who had never used TZDs. Patients who had used TZDs were significantly younger, had a higher body mass index, were less likely to have had a prior fracture, and less likely to have had recent cardiovascular disease.

After adjustment for diabetes duration, prior CVD, baseline and time-dependent exposure to other medications, and BMI, the rate of fracture per cumulative year of TZD exposure was significantly elevated for hip fracture in both men (hazard ratio, 1.14) and women (HR, 1.17) and for distal fracture in women (1.16).

In the self-controlled case series, the incidence rate ratio comparing the exposed and unexposed periods of time for

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each individual patient demonstrated a significantly increased risk of hip fractures during the period of TZD exposure for the group as a whole (incidence rate ratio, 1.98) and in both men (2.23) and women (1.9). The risk for distal fractures was significantly greater for the entire group (1.4) and for women (1.57) but was not significant among men.

The incidence rate ratio by duration of TZD exposure rose from 1.45 at less than 1 year to 3.59 after 6 years of exposure, Dr. Colhoun reported.

The overall relative risk in the self-controlled case series of approximately 2 and a current prevalence of exposure of about 20% implies that about 17% of fractures in patients with diabetes could be attributable to TZDs, she noted.

Of note, she added, this analysis assumes that the absence of TZDs would not result in more use of another agent that also increases fracture risk such as insulin. Studies are underway to assess that further and to build a predictive model of fracture in diabetes. Other studies are looking at whether reducing the TZD dose might lower the fracture risk, and whether the risk goes away when the drug is stopped. Preliminary data suggest that the risk remains high, she said.

Wellcome Trust Scottish Health Informatics Programme and the Chief Scientist's Office, Scotland, funded the study. Dr. Colhoun disclosed that she has received research support from Pfizer, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Roche. She serves on the speakers bureau for Pfizer, is a board/advisory panel member for Eli Lilly, and owns stocks/shares in Roche.

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

**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.\* 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 <sup>a</sup> =2573) Percent	Fluzone (N <sup>a</sup> =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

<sup>a</sup>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 <sup>a</sup> =2573) Percent	Fluzone (N <sup>a</sup> =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

Rx only

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

	Fluzone High-Dose (N <sup>a</sup> =2573) Percent	Fluzone (N <sup>a</sup> =1260) Percent
<b>Fever</b>		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

<sup>a</sup>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, 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.<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

	GMT		GMT Ratio	Seroconversion % <sup>a</sup>		Difference	Met Both Pre-defined Endpoints? <sup>2</sup>
Influenza Strain	Fluzone High-Dose N <sup>a</sup> =2576	Fluzone N <sup>a</sup> =1275	Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N <sup>a</sup> =2576	Fluzone N <sup>a</sup> =1275	Fluzone High-Dose minus Fluzone (95% CI)	
<b>A (H1N1)</b>	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
<b>A (H3N2)</b>	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
<b>B</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>a</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>b</sup>N is the number of subjects in the Immunogenicity Analysis Set.

<sup>c</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

1. 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 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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