CLINICAL

Flu Vaccine Coverage

Efforts to direct influenza vaccine to priority groups during the 2004-2005 vaccine shortage were "somewhat" successful, according to the Centers for Disease Control and Prevention.

Vaccination coverage for all groups nationwide in 2004-2005 declined 46% from the 2003-2004 period, with the greatest decreases in younger people (51% in those aged 50-54 vs. 41% in those aged 60-64) and in people with self-reported good health; coverage dropped 52% in those with "excellent" health, 35% in those with

CAPSULES

"fair" health, and 24% in those with "poor" health.

The findings were based on an analysis of data that were sampled from the 70 million members of the 250 managed care organizations in the Consumer Assessment of Health Plans survey (MMWR 2005;54:921-3).

The substantial decreases observed in vaccination coverage among those with fair or poor health in this population are of concern.

Research regarding medical conditions associated with self-reporting of fair or

poor health could help develop tools for managing future vaccine shortages, the CDC noted.

Flu Vaccine Efficacy

Elderly patients in long-term care facilities appear to get the most benefit from flu vaccination, whereas those in the community receive only modest benefits, Tom Jefferson, FFPHM, of the Cochrane Vaccines Field in Allesandria, Italy, and his colleagues reported.

The investigators reviewed data from 64 studies of influenza vaccine effectiveness and found that the effectiveness of wellmatched vaccines in areas with high viral circulation was 23% against flulike illness. Such vaccines in this setting were not significantly effective against influenza, but vaccine effectiveness (VE) was 46% for preventing pneumonia, 45% for preventing hospital admission for influenza and pneumonia, 42% for preventing death associated with influenza or pneumonia, and 60% for reducing all-cause mortality (Lancet 2005;366:1165-74).

In elderly people living in the community, well-matched vaccines were not significantly effective against influenza, influenza-like illness, or pneumonia, but adjusted VE was 26% for preventing death from influenza and pneumonia, 29% for preventing hospital admissions for all respiratory illnesses, and 47% for reducing allcause mortality.

Efforts should concentrate on increasing vaccination coverage in long-term care facilities, on assessing the effect of vaccination in high-risk groups, and on developing better vaccines by incorporating improved knowledge of influenza-like illnesses in different communities, the investigators concluded.

Flu Vaccine Development

The National Institute of Allergy and Infectious Diseases and MedImmune Inc. together will develop vaccines against avian influenza viruses that could cause pandemics, according to the Department of Health and Human Services.

The agreement was prompted by concerns that the viruses could acquire the ability to spread efficiently from person to person and cause a global outbreak.

The two organizations will develop at least one vaccine for each of 16 variations of hemagglutinin, a key influenza surface protein. One priority is development of a vaccine against the H5N1 virus, which has spread rapidly among birds and other animals in Asia over the past 2 years and has affected at least 115 people throughout Asia. The collaborative effort could take years, but will help in preparing for future influenza pandemics, the HHS stated.

Oyster-Related Gastroenteritis

An outbreak of Vibrio parahaemolyticus infection linked with Alaskan ovsters has extended the northernmost documented source of such oyster-related illness by 1.000 km.

Rising ocean water temperatures appear to have contributed to the outbreak, which occurred among cruise ship passengers, Joseph B. McLaughlin, M.D., of the Alaska Department of Health and Social Services and his colleagues reported.

A retrospective cohort study of 132 passengers showed that raw-oyster consumption was the only significant predictor of illness (adjusted odds ratio 5.2). An environmental analysis showed that most of the oysters associated with the outbreak were harvested from a single farm with mean daily water temperatures frequently over 15.0° C during July and August harvesting. This temperature is believed to be the threshold for the risk of V. parahaemolyticus infection (N. Engl. J. Med. 2005;353:1463-70).

Control measures, including monitoring for V. parahaemolyticus, should be considered when water temperatures at oyster farms exceed 15° C, the investigators said.

-Sharon Worcester

BONIVA® (ibandronate sodium) TABLETS BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

- CONTRAINDICATIONS

 Known hypersensitivity to BONIVA or to any of its excipients

 Uncorrected hypocalcemia (see PRECAUTIONS: General)

 Inability to stand or sit upright for at least 60 minutes

 (see DOSAGE AND ADMINISTRATION)

Inability to stand or sit upright for at least 60 minutes (see DOSAGE AND ADMINISTRATION)

WARNINGS
BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS: General

Mineral Metabolism: Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects: Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment: BONIVA is not recommended for use in patients with

with BOWNA. Inertore, patients should be advised to pay particular attention to and be able to comply with the doising instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment BOWNA is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corificosteroids), and co-morbid disorders (eg, anemia, caagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis of the Jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefitrisk assessment. Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/ or muscle pain has been reported in patients taking bisphosphonates that are apprived for the prevention and treatment of esteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include BONIVA (labandronate sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of symptoms were similar in the BONIVA and placebo groups.

Information Leaflet carefully before taking BONIVA to re-r

studies with BONIVA, the percentages of patients with these symptoms were similar in the BONIVA and placebo groups.

Information of Patients. Patients should be instructed to read the Patient Information Leaflet carefully before taking BONIVA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

-BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medications containing multivalent cations (including antacids, supplements or vitamins).

-To facilitate delivery to the storanch, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 ac) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.

-Patients should not chew or suck the tablet because of a potential for coropharyngeal ulceration.

-The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).

-If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient's bould then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

original schedule.

The patient must not take two 150-mg tablets within the same week. If the patients next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until their next scheduled BONIVA day to take their tablet. The patient must wait until their next scheduled BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule. Patients should receive supplemental calcium and vitamin D for dietary intake is inadequate. Intake of supplemental calcium and vitamin is 10 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.

absorption of Bowlay.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

snew or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn. **Drug Interactions**Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA BONIVA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see **PRECAUTIONS**: Information for **Patients**).

PRECAUTIONS: Information for **Patients Drug/Laboratory Test Interactions: Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

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refinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: In a 104-ek carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered oral gavage to male and female Wistar rats (systemic exposures up to 12 and 7

times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUIC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to male and female NMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUIC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUIC comparison). A observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended done or administered to make a statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUIC comparison). The relevance of these findings to humans is unknown.

Mutagenesis: There was no evidence for a mutagenic or clastogenic potential of bandronate in the following assays: in vitro bacterial mutagenesis assay in Chinese hamster V79 cells, and chromosomal abernation test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in wwo mouse micronucleus tests for chromosomal damage.

**Impairment of Fertility Cereos Literated from 14 days prior to mating hrounds.

mutagenesis assay in Chinese hanster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal dameral in properties. In vivo mouse micronucleus tests for chromosomal dameral in fertility. Corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 15 mg hased on AUC comparison).

Pregnancy: Pregnancy Category C: In female rats given oral doses of 1,4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deatits were observed at the time of delivery in all dose groups (3 times human exposure at the recommended daily oral dose of 2.5 mg or 1 times human exposure at the recommended daily oral dose of 2.5 mg or 1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Was likely related to maternal dystoca. In pregnant rats given oral doses of 6. 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and persparturient mortality in any of the treated groups (16 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation lose was observed in at Streated from 14 days before mating through teaching or 46 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). In the subserved in a first breated from 14 days before mating through teaching or 46 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Pregnant rats dosed oral by subserved in a first breated from 14 days before matin

potential risk to the mother and fetus.

Nursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/ml. from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, cution should be exercised when BONIVA is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

established.

Geriatric Use: Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving BONIVA 150 mg once monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

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Daily Dosing: Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis: Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIWA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIWA 2.5 mg daily group and the placebo group. Overall, and according to body system, there was no difference between BONIWA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 1 lists adverse events from the Treatment and Prevention Studies reported in 2% of patients and in more patients treated daily with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality. Table 1: Adverse Events Occurring at a Frequency 2% and in More Patie

Osteoporosis Treatment and Prevention Studies				
Body System	Placebo	BONIVA 2.5 mg		
	%	%		
	(n=1134)	(n=1140)		
Body as a Whole				
Back Pain	12.2	13.5		
Pain in Extremity	6.4	7.8		
Infection	3.4	4.3		

Table 1 cont.				
Asthenia	2.3		3.5	
Allergic Reaction	1.9		2.5	
Digestive System				
Dyspepsia	9.8		11.9	
Diarrhea	5.0		6.8	
Tooth Disorder	2.3		3.5	
Vomiting	2.1		2.7	
Gastritis	1.9		2.2	
Metabolic and Nutritional Dis				
Hypercholesterolemia	4.2		4.8	
Musculoskeletal System				
Myalgia	5.1		5.7	
Joint Disorder	3.3		3.6	
Arthritis	2.7		3.2	
Nervous System				
Headache	5.8		6.5	
Dizziness	2.6		3.7	
Vertigo	2.5		3.0	
Nerve Root Lesion	1.9		2.2	
Respiratory System				
Upper Respiratory Infection	33.2		33.7	
Bronchitis	6.8		10.0	
Pneumonia	4.3		5.9	
Pharyngitis	1.5		2.5	
Urogenital System				
Urinary Tract Infection	4.2		5.5	
Once-Monthly Dosing: In a	1-vear	double-blind	multicenter study co	mnaring

Once-Monthly Dosing: In a 1-year double-blind, multicenter study comparing BONIWA 2.5 mg once daily and BONIWA 150 mg once monthly in women with postmenopausal osteoporosis, the overall safety and blerability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the BONIWA 2.5 mg daily group and 7.7% in the BONIWA 150 mg once-monthly group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the BONIWA 2.5 mg daily group and 7.8% in the BONIWA 150 mg once-monthly group. Table 2 lists the adverse events reported in 2% of patients without attribution of causality.

Table 2: Adverse Events with than Incidence of at Least 2% in Patients Treated

Table 2: Adverse Events with an Incidence of at Least 2% in Patients Treate with BONIVA 150 mg Once Monthly or 2.5 mg Daily				
Body System/Adverse Event	BONIVA	BONIVA		
	2.5 mg daily	150 mg monthly		
	%	%		
	(n=395)	(n=396)		
Vascular Disorders				
Hypertension	7.3	6.3		
Gastrointestinal Disorders				
Dyspepsia	7.1	5.6		
Nausea	4.8	5.1		
Diarrhea	4.1	5.1		
Constipation	2.5	4.0		
Abdominal Pain ^a	5.3	7.8		
Musculoskeletal and Connective				
Arthralgia	3.5	5.6		
Back Pain	4.3	4.5		
Pain in Extremity	1.3	4.0		
Localized Osteoarthritis	1.3	3.0		
Myalgia	0.8	2.0		
Muscle Cramp	2.0	1.8		
Infections and Infestations				
Influenza	3.8	4.0		
Nasopharyngitis	4.3	3.5		
Bronchitis	3.5	2.5		
Urinary Tract Infection	1.8	2.3		
Upper Respiratory Tract Infection	2.0	2.0		
Nervous System Disorders				
Headache	4.1	3.3		
Dizziness	1.0	2.3		
General Disorders and Administr				
Influenza-like Illness ^b	0.8	3.3		
Skin and Subcutaneous Tissue D				
Rash ^c	1.3	2.3		
Psychiatric Disorders				
Insomnia	0.8	2.0		

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Ratents with a previous history of gastrointestinal disease, including patients with peptic ulcer without recent bleeding or hospitalization and patients with dyspesia or reflux controlled by medication, were included in the once-monthly treatment study. For these patients, there was no difference in upper gastrointestinal adverse events with the 150 mg once-monthly regimen compared to the 2.5 mg once-daily regimen.

Coular Adverse Events: Reports in the medical literature indicate that bisphosphonates may be associated with coular inflammation such as uveits and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily. Two patients who received BONIVA once monthly experienced ocular inflammation, one was a case of usefuls and the other scleritis.

Laborator Vest Findings: In the 3-vear treatment study with BONIVA 2.5 mg daily.

inflammation, one was a case of weltis and the other scleritis.

Laboratory Test Findings: In the 3-year treatment study with BONIVA 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate breatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory abnormatities indicative of hepatic or cenal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no changes were noted for the 150 mg once-monthly administration in the 1-year study.

Were roced for the 20 mig order-information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as usest stomach, dyspepsia, esophagitis, gashtils, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.



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