### CLINICAL CAPSULES

## **Gastric Bypass Alters Gut Hormones** Gastric bypass surgery, unlike gastric banding, alters gut hormones that favor satiety and long-term changes in body weight.

Formerly obese patients who had undergone Roux-en-Y gastric bypass had increased levels of peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) and exaggerated insulin responses immediately following a meal. "None of these effects were observed in patients losing similar amounts of weight through gastric banding, suggesting that the hormonal changes are not secondary to weight loss alone,"

said Dr. Carel W. le Roux, of Imperial College London, and colleagues (Ann. Surg. 2006;243:108-14).

Released postprandially from the distal gastrointestinal tract, PYY inhibits the release of a neuropeptide that stimulates food intake. GLP-1 promotes postprandial insulin release and improves pancreatic β-cell function. GLP-1 has also been reported to inhibit food intake in humans.

The researchers compared plasma levels of PYY, GLP-1, and ghrelin after a 420-kcal meal in 15 lean control subjects, 12 obese control subjects, 6 patients who had undergone Roux-en-Y gastric bypass, and 6 patients who had undergone gastric banding. The surgery patients underwent the procedures 6-36 months prior to the measures.

Roux-en-Y bypass patients had an exaggerated GLP-1 response at 30 minutes-230% of the baseline value. In contrast, normal controls, obese controls, and gastric banding patients had GLP-1 responses at 30 minutes of 66%, 22%, and 50% above baseline.

Likewise, Roux-en-Y bypass patients had an exaggerated PYY response at 90 minutes-162% of baseline. Normal controls, obese controls, and gastric banding ites

# **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 us 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 gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastrointestinal 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 as 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 DOSAEE AND ADMINISTRATION).
 Severe Renal Impairment: BONIVA is not recommended for use in patients with severe renal Impairment (carbin dearance -30 mL/min).
 Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Moown risk, factors for osteonecrosis include a diagnosis or cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, amenia, coagujoatity, infection, pre-existing dental disease). Moorn risk factors for patients treated orally. For patients with develog osteonecrosis of the jaw (MNJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients treated orally. For patients with develog osteonecrosis of th

patient based on individual benefit/risk assessment. Musculoskeletal Parin. In postmarketing experience, severe and occasionally incapacitating bone, joint, and/ or muscle pain has been reported in patients taking bisphosphomates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include BONNA (bandronate sodium) Tables. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. In placebo-controlled studies with BONNA, and placebo groups.

Studies with BONNA, the precentages of patients with these symptoms were similar in the BONNA and placebo groups.
 Information for Patients: Patients should be instructed to read the Patient Information Leaflet carefully before taking BONNA, 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.
 -BONNA 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 stomach, and thus reduce the potential for esophageal irritation. BONNA tablets should be taken with group or position. Patients should not be down for 60 minutes after taking BONNA.
 -Plain water is the only drink that should be taken with BONNA. 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 corpharyngeal ulceration.
 -The BONNA tablet, the patient is water, and the patient's next scheduled BONNA day.
 -If the nonce-monthy dose is missed, and the patient's next scheduled BONNA tablet.
 -Rom tablet in the morning following the date that its remembered (see DOSAGE AND ADMINISTRATION). The patient should be instructed to take one BONNA 150-mg tablet should be the taken the return to taking one BONNA tablet.
 -The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONNA is only to 7 days away, the patient must wait the the interture the interture taken the patient's next scheduled BONNA table the patient'

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 should then return to taking one 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 should be dlayed for at least 60 minutes following or al administration of BONIVA in order to maximize absorption of BONIVA.

absorption of BUNIVA. 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.

Seek inducta data pain or swallowing, retrosternal pain, or hearbitum. Drug Interactions Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONNA BONNA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONS: Information for Patients). H 2 Blockers and Proton Pump Inhibitors (PPK): Of over 3500 patients enrolled in the BONNA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPs), Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of oupper gastrointestinal adverse experiences in the patients the incidence of upper gastrointestinal adverse experiences in the patients the incidence of upper gastrointestinal adverse experiences in the patients treated with BONNA 150 mg once monthly was similar to that in patients treated with BONNA 2.5 mg once daily. ApplinANDATERICAL The incidence of upper gastrointestinal adverse events in patients treated with badronate 2.5 mg daily (2.8 %) was similar in that in patients. The incidence of upper gastrointestinal events in patients concomitantly taking apptin or NSAID was similar in patients taking alphane taken by 20% of the 1602 patients. The incidence of upper gastrointestinal events in patients concomitantly taking apptin or NSAID was similar in patientstaking landronate Drug/Laboratory Test Interactions: Bisphosphonates are known to interfer with the use of bone-imaging agents. Specific studies with ibandronate have no been performed.

ren perionieu. **arcinogenesis, Mutagenesis, Impairment of Fertility:** *Carcinogenesis*: In a 104-eek 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 AUC 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 AUC 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 monthy exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day vere administered buman exposure at the recommended once-monthly oral dose of 150 mg, based on AUC 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 witho bacterial mutagenesis assay in Salmonella typhimurium and Escherichia coli (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human explosation test in the was traditive cover biek work and chromosomal aberration test in human exploration test in the recommended fallings to humans.

Comparison was needed and the set of the set

obtential risk to the mother and fetus. Wursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, bandronate 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 Jacama concentrations. It is not known whether BOIWA is excerted in human milk. Because many drugs are excreted in human milk, caution should be exercised when 30NWA is administered to a nursing woman. Pediatric Use: Safety and effectiveness in pediatric patients have not been schaling and the safety and effectiveness in pediatric patients have not been

common use. Sarcy and energineers in pediatric patients have not been 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 monthy 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 FEACTIONS 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.

Beefit profile to DOTIVE 2.5 ing Grec damp in tacco datases the activity 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 BONIVA 2.5 mg daily group. The percentage of placebo activity of the BONIVA 2.5 mg daily group. The percentage of plateints who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group. Overall, and according to body system, there was no difference between BONIVA 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 22% of platents 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 Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the 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		

patients had I	PYY r	esponses at 90 minut
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Table 1 cant		
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	orders	
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
		ble-blind, multicenter study comparing
BUNIVA 2.5 mg once daily ar	IG RONIVA	150 mg once monthly in women with
postmenopausal osteoporosis, tr	e overall sa	fety and tolerability profiles of the two oral

postmenopausal osteoporosis, the overall safety and tolerability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the BONIVA 2.5 mg daily group and 7.1% in the BONIVA 150 mg once-monthy group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the BONIVA 2.5 mg daily group and 7.8% in the BONIVA 150 mg once-monthy group. **Table 2** lists the adverse events reported in 2% of patients without attribution of causality.

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 <sup>a</sup>	5.3	7.8
Musculoskeletal and Connective Tis	ssue Disorders	
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
Músčle 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 Administrati	on Site Conditions	
Influenza-like Illness <sup>b</sup>	0.8	3.3
Skin and Subcutaneous Tissue Disc	orders	
Rash <sup>c</sup>	1.3	2.3
Psychiatric Disorders		

Combination of abdominal pain and abdominal pain upper Combination of influenza-like illness and acute phase reaction Combination of rash purtici, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema

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Inflammation, one was a case of uveits and the other scientis. 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 bisphosphonather teratment, 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 abnormalities indicative of hepatic renal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no changes were noted for the 150 mg once-monthly administration in the 1-year study. MERDINGACE, No specific incidence of the second sec

Were noted for the 150 mg once-monithy administration in the 1-year study. OVERDOSAGE. No specific 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 upset stomach, dyspensia, esophaglis, gastritis, or uicer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophagea irritation, vomiting should no the induced, and the patient should remain fully upright. Dialysis would not be beneficial. Distributed by:

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e Moore Drive search Triangle Park, NC 27709 Issued: March 2005 Copyright © 2005 by Roche Laboratories Inc. All rights reserved of 49%, 14%, and 22% above baseline.

"The higher postprandial PYY response after gastric bypass surgery ... may contribute to the patients' increased satiety and weight loss." Increased GLP-1 might contribute to immediate improvements in glycemic control.

Obese subjects had a lower fasting ghrelin level (446 pmol/L), compared with lean subjects (700 pmol/L). There were no differences in the fasting ghrelin levels among the obese and surgically-treated groups. Ghrelin stimulates food intake.

### Albuminuria, Central Fat in Diabetes

Microalbuminuria and macroalbuminuria appear to occur more often in men with type 1 diabetes than in women with the disease because men have more visceral fat, according to findings from a cross-sectional follow-up study.

Further studies will be necessary to determine the cause of the association between male gender and increased albumin excretion rate (AER), because central obesity itself may not cause the increased excretion, reported Dr. Shalamar D. Sibley of the University of Minnesota, Minneapolis, and associates (Am. J. Kidney Dis. 2006;47:223-32).

The study involved 1,185 patients with type 1 diabetes who participated in the Epidemiology of Diabetes Interventions and Complications trial. After 4 years of follow-up, 217 patients developed an elevated AER: 163 had microalbuminuria and 54 had macroalbuminuria.

Waist-to-hip ratio was significantly and independently associated with elevated AER in men, but not in women, after adjusting for age, HbA1c level, smoking status, duration of diabetes, and systolic blood pressure.

## Hyperparathyroidism Impairs Respiration

Researchers in Turkey have reported greatly improved respiratory measures after surgical removal of parathyroid adenomas or subtotal parathyroid excision in patients with hyperparathyroidism.

Investigators with the Istanbul Medical Faculty measured forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) before surgery and 6 months after surgery in 15 patients with symptomatic hyperparathyroidism. A group of 10 euthyroid patients with multinodal goiter undergoing near total thyroidectomy served as controls.

Dr. Yasemin Giles and colleagues found that preoperative FVC values were below reference values in 11 of 15 patients (73%) and FEV1 values were below reference values in 9 of the 15 patients (60%) with hyperparathyroidism (Arch. Surg. 2005;140: 1167-71).

Respiratory function was normal before and after surgery in controls. Patients with symptomatic hyperparathyroidism did not have dyspnea before surgery, but all reported fatigue, weakness, and exhaustion with minimal effort.

Improvement in respiratory function was "found to have a linear correlation with preoperative total serum calcium," the investigators wrote.

Surgery resulted in normalization of serum calcium in all patients. Symptomatic disease is linked to hypercalcemia, they noted.