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## Dilatation, History Both Predict Preterm Birth

BY BETSY BATES

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RENO, NEV. — Cervical dilatation at presentation and over the 6 hours following admission was highly predictive of preterm birth in women admitted with preterm labor, but obstetric history also contributed important information about which mothers were likely to deliver before 34 weeks' or 37 weeks' gestation.

Dr. Jamie A. Bastek and associates in the

department of obstetrics and gynecology at the University of Pennsylvania, Philadelphia, reviewed the records of 400 women with singleton pregnancies who were admitted in preterm labor before 34

The researchers sought to determine whether the risk of preterm birth could be stratified based on a number of easily identifiable variables, including cervical dilatation and a prior history of preterm

Dr. Bastek presented their results at the annual meeting of the Society for Gynecologic Investigation.

"As tocolytics are not without harm, we felt it was important to see if we could identify women with a low likelihood of preterm birth who could be managed without admission and/or tocolytic agents" she said in an interview at the meeting, where the study was presented in poster form.

As expected, the total cohort had a sig-

nificant risk of early delivery.

Nearly 45% delivered before 34 weeks, and 63% delivered before 37 weeks' ges-

In trying to determine what distinguished the women who delivered after 37 weeks, Dr. Bastek and associates found a number of features conferring protection, including later gestational age at presentation, less cervical dilatation at presentation, smaller rates of change in cervical dilatation, and obstetric history.

FOSAMAX PLUS D<sup>™</sup> (alendronate sodium/cholecalciferol) Tablets BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia

- Inability to stand or sit upright for at least 30 minutes

Inability to stand or sit upright for at least 30 minutes
Hypersensitivity to any component of this product
Hypocalcemia (see PRECAUTIONS, General)
WARNINGS
FOSAMAX PLUS D, like other bisphosphonate-containing products, may cause local irritation of the upper gastrointestinal mucosa. Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs. juired hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX PLUS D and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn. The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX PLUS D and/or who fail to swallow it with a full glass (6-8 oz) of water, and/or who continue to take FOSAMAX PLUS D after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that toms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX PLUS D should be used under appropriate supervision. Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX PLUS D is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodentits, or ulcers). There have been post-marketing reports of gastric and funderal ulcers with alendronate, some severe and with complications. duodenal ulcers). There have been post-marketing reports of gastric an duodenal ulcers with alendronate, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General. Causes of experience.

PRECAUTIONS

General. Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered. Alendronate Sodium: Hypocalcemia must be corrected before initiating therapy with FOSAMAX PLUS D (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX PLUS D. Presumably due to the effects of alendronate on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur. Cholecalcifus/IFOSAMAX PLUS D alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D level below 9 ng/mL). Patients at increased risk for vitamin D insufficiency (e.g., those who are nursing home bound, chronically ill, over the age of 70 years) should receive vitamin D supplementation in addition to that provided in FOSAMAX PLUS D. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and FOSAMAX PLUS D. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered. Vitamin D<sub>3</sub> supplementation may worsen hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of 1,25 dihydroxyvitamin D (e.g., leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients. Mussculoskeltal Pain: In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes FOSAMAX® (alendronate sodium). 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 clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups. Dental: Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often similar in the Posawikk and piceure discount of period. Used infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, con-Known risk factors for osteoneorosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection). Patients who develop osteoneorosis of the jaw (DNJ) while on bisphosphonate therapy should receive care by an oral surgeon. 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 for DNJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. <u>Renal.</u> insufficiency: FOSAMAX PLUS D is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

renal insufficiency (creatinine clearance <35 mL/min). (See DUSAGE AND ADMINISTRATION.)

Information for Patients. \*\*General\*\* Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX PLUS D and to reread it each time the prescription is renewed. Patients should be instructed to take supplemental calcium if intake is inadequate. Patients at increased risk for Vitamin D insufficiency (e.g., those who are unrising home bound, chronically ill, over the age of 70 years) should be instructed to take additional vitamin D. Patients with gastrointestinal malab sorption syndromes should be informed that they may require additional vitamin D supplementation. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist. \*\*Dosing Instructions\*\* Patients should be instructed that the expected benefits of FOSAMAX PLUS D may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first flood, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alennirst 100d, neverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX PLUS D with a full glass of water (6-8 oz) and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening hearthurn) they should stop taking FOSAMAX PLUS D and consult their physician. Patients should be instructed that if they miss a dose of FOSAMAX PLUS D, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week as originally scheduled on they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day. *Drug Interactions (also see CLINICAL PHARMACOLO-GY. Pharmacokinetiss, Drug Interactions): Alendronate Sodium—Estrogen/hormone replacement therapy (HRT).* Concomitant use of HRT (estrogen ± progestin) and FOSAMAX® (alendronate sodium) was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by minnowever, the degree of suppression of none tumover (as assessed by mini-eralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHAR-MACOLLOGY, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy, (HRT) and ADVERSE REACTIONS, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy). Calcium Supplements/Antacids. It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate. Therefore additions will write talest one-half hour after taking ETSAMAX herefore, patients must wait at least one-half hour after taking FOSAMAX Intereore, patients must walt at least one-hair nour arter taking PUSAMIAP. PLUS D before taking any other oral medications. Aspirin. In clinical studies, the incidence of upper gastrointestinal adverse events was increased patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products. Nonsteroidal Anti-inflammatory Drugs (NSAIDs). FOSAMAX PLUS D may be administered 1 patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of unper pastrointestinal adverse events was similar in patients incidence of upper gastrointestinal adverse events was similar in patietaking FOSAMAX 5 or 10 mg/day compared to those taking placebo. taking POSAWIAA S or 10 mg/ud 20 milpateu to mose taking piacebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX PLUS D. Cholecalofferol— Drugs that may impair the absorption of cholecalofferol. Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the absorption of vitamin D. Drugs that may increase the catabolism of cholecalciferol. Anticonvulsants, cimetidine, and this side as experimental contents.

increase the catabolism of cholecalciferol. Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D. Carcinogenesis, Mutagenesis, Impairment of Fertility. The following data are based on findings for the individual components of FOSAMAX PLUS D. Alendronate Sodium: Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 1.2 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m². The relevance of this finding to humans is unknown. Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (n=0.003) in a 2-vear oral carcinogenicity finding to humans is unknown. Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area mg/m². The relevance of this finding to humans is unknown. Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vitro* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in chieses hamster ovan cells however alendronate vivo chromosomal aberration assay in mice. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results. Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m²). Cholecalcifero!. The carcinogenic potential of cholecalciferol (vitamin D<sub>2</sub>) has not been studied in rodents. Calcitrio!, the hormonal metabolite of cholecalciferol, was not genotoxic in the Ames microbial mutagenesis assay with or without metabolic activation, and in an in vivo micronucleus assay in mice.
Ergocalciferol (vitamin D<sub>2</sub>) at high doses (150,000 to 200,000 IU/kg/day) administered prior to mating resulted in altered estrous cycle and inibilition inibilition. administered prior to mating resulted in altered estrous cycle and inhibition of pregnancy in rats. The potential effect of cholecalciferol on male fertility

or pregnancy in rats. The potential effect of cholecalciterol on male fertility is unknown in rats. **Pregnancy.** Pregnancy Category C: Alendronate Sodium— Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day stand decreased body weight gain in normal pups at 1 mg/kg/day. Site of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m². No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m²) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (1.0.13 times a 40 mg human daily dose based on surface area, mg/m²) when rats were treated from before mating through gestation. mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m²) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during garly, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths. Bisphosphonates are incorporated into the hone matrix, from which they are oradually released over a period of years. maternal, but not fetal deaths. Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into audit bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied. Cholecalciferol— No data are available for cholecalciferol (vitamin D<sub>3</sub>). Administration of high doses (≥10,000 IU/dvery other day) of ergocalciferol (vitamin D<sub>3</sub>) to pregnant rabbis; resulted in abortions and an increased incidence of fetal aortic stenosis. Administration of vitamin D<sub>2</sub> (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased fetal weight, and impaired osteogene-

sis of long bones postnatally. There are no studies in pregnant women. FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

\*\*Nursing Mothers.\*\* Cholecalciferol and some of its active metabolites pass into breast milk. It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX PLUS D is administered to nursing women.

\*\*Postativit les.\*\* Soften and effectivenese in predictive pricing beaue on been Pediatric Use. Safety and effectiveness in pediatric patients have not been

exercised when FOSAMAX PLUS D is administered to nursing women. Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use. Of the patients receiving FOSAMAX® (alendronate sodium) in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, and osteoporosis studies in men (see CLINICAL PHARMACOLOGY, Clinical Studies), 45% and 54%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dietary requirements of vitamin D₂ are increased in the elderly.

ADVERSE REACTIONS

Clinical Studies. FOSAMAX: In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy. FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies. Treatment of soteoporosis — Postmenopausal women in clinical studies. Treatment of soteoporosis — Postmenopausal women. In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 196 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with either FOSAMAX (10 mg/day for 3 years, n=196) or patients placebo (n=397) for the United States/Multinational Studies were Gastrointestinal: abdominal pain 6.6% and 4.8%, nausea 3.6% and 4.0%, dyspepsia 3.6% and 3.5%, constipation 3.1% and 1.8%, diarrhea 3.1% and 1.8%, flatulence 2.6% and 0.5%, acid regurgitation 2.0% and 4.3%, esophageal ulcer 1.5% and 0.0%, vomiting 1.0% and 1.5%, dysphagia 1.0% and 0.0%, abdominal distention 1.0% and 0.8%, gastritis 0.5% and 1.3%; Musculoskeletal: musculoskeletal (bone, muscle, joint) pain 4.1% and 2.5%, muscle cramp 0.0% and 1.0%; ilervous 5/stem/Psychiatric: headache 2.6% and 1.5%, dizziness 0.0% and 1.0%; and Special Senses: taste perversion 0.5% and 1.0%, respectively. For the Fracture Intervention Trial, with ether FOSAMAX (5 mydday for 2 years and 10 mg/day for either or 2 additional years, n=3236) or placebo (n=3223), corresponding val-ues were Gastrointestinal: abdominal pain 1.5% and 1.5%, nausea 1.1% and 1.5%, dyspepsia 1.1% and 1.2%, constipation 0.0% and 0.2%, diarues were Gastrointestinal: abdominal pain 1.5% and 1.5%, nausea 1.1% and 1.5%, dyspepsia 1.1% and 1.2%, constipation 0.0% and 0.2%, diatriea 0.6% and 0.3%, falcituence 0.2% and 0.3%, acid regurgitation 1.1% and 0.9%, esophageal ulcer 0.1% and 0.1%, vomiting 0.2% and 0.3%, dysphagia 0.1% and 0.1%, abdominal distention 0.0% and 0.0%, gastritis 0.6% and 0.7%; Musculoskeletal: musculoskeletal (bone, muscle, joint) pain 0.4% and 0.3%, muscle cramp 0.2% and 0.1%; Nervous 5ystem/Psychiatric: headache 0.2% and 0.1%, dizziness 0.0% and 0.1%; and Special Senses: taste perversion 0.1% and 0.0%, respectively. Rarely, rash and erythema have occurred. One patient treated with FOSAMAX (10 mg/day), which was considered drug related. Aspirin and Vosaminage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered. The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study. In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg/dis/ (n=370) were similar. The adverse experiences considered by the acyperience was similar to that outning the first lines years of the Study, in one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group were *Gastrointestinal*: abdominal pain 3.7% and 3.0%, dyspepsia 2.7% and 2.2%, acid regurgitation 1.9% and 2.4%, nausea 1.9% and 2.4%, abdominal distention 1.0% and 1.4%, constipation 0.8% and 1.6%, flatulence 0.4% and 1.6%, gastritis 0.2% and 1.1%, gastric ulcer 0.0% and 3.2%; and *Musculoskeletal*: musculoskeletal (bone, muscle, joint) pain 2.9% and 3.2%, and muscle cramp 0.2% and 1.1%, respectively. *Men*. In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience year 2.7% for FOSAMAX 10 mg/day (n=146) vs. 10.5% for placebo (n=95), and 6.4% for once weekly FOSAMAX 70 mg (n=109) vs. 8.6% for placebo (n=58). The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo for the two-year study were *Gastrointestinal*: acid regurgitation 4.1% and 3.2%, flatulence 4.1% and 1.1%, gastroesophageal reflux disease 0.7% and 3.2%, flatulence 4.1% and 1.1%, gastroesophageal reflux disease 2.8% and 0.0%, tyspepsia 3.4% and 0.0%, dispersively; for the one-year study, the adverse experiences were *Gastrointestinal*: acid regurgitation 0.0% and 0.0%, dispersional and 0.0%, espectively; *Concomitant use with estrogen/hormone replacement therapy*. In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the

FOSAMAX® (alendronate sodium) for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day (n=642) and place-bo (n=648) were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo. In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 5 mg (n=362) and FOSAMAX 5 mg daily (n=361) were similar. The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with FOSAMAX 5 mg/day or placebo for the two- or three-year studies were *Gastrointestiniat* (syspepsia 1.9% and 1.4%, advominal pain 1.7% and 3.4%, acid regurgitation 1.4% and 2.5%, nausea 1.4% and 1.4%, diarrhea 1.1% and 1.7%, constipation 0.9% and 0.5%, abdominal distention 0.2% and 0.3%; and *Musculoskeletal*: musculoskeletal (bone, muscle or joint) pain 0.8% and 0.9%, respectively. For the one-year study with FOSAMAX 5 mg/day and once weekly FOSAMAX 5 mg, corresponding values were *Gastrointestinal*: dyspepsia 2.2% and 1.7%, abdominal pain 4.2% and 2.2%, acid regurgitation 4.2% and 4.7%, nausea 2.5% and 1.4%, diarrhea 1.1% and 0.6%, constipation 1.7% and 0.3%, abdominal distention 1.4% and 2.2%, respectively. *Treatment of glucocorticoid-induced osteoporosis*. In two, one-year placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 mg (rate) and 1 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 mg/day (n=161) or FOSAMAX 10 mg/day (n=157) or placebo (n=159) were *Gastrointestinal*: abdominal pain 1.9%, 3.2%, and 0.0%; acid regurgitation 1.9%, 2.5%, and 1.3%; constipation continued therapy for patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo. Laboratory Test Findings— In double-blind, multicenter, controlled studies, expentionative mild and treajent decreases in serum calcium and place. Laboratory Test Findings— In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups. FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol): In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 7.0 m

In osteoporotic postmenopausal women (n=652) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

Post-Marketing Experience. The following adverse reactions have been reported in post-marketing use with alendronate: Body as a Whole; hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema. Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulcers, and DoSAGE AND ADMINISTRATION). Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental). Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain); joint swelling. Nervous system; distriction servers and vertigo. Skir: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Special Senses: rarely uveitis, scleritis or episcleritis.

For more detailed information, please read the Prescribing Infor FOSAMAX PLUS D is a trademark of Merck & Co., Inc. FOSAMAX is a registered trademark of Merck & Co., Inc.



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Presentation at fewer than 25 weeks' gestation conferred more than a 15-fold increase in the odds of delivering before 34 weeks, compared with women who presented at 32 weeks' gestation. Presentation before 28 weeks was also a noteworthy risk, bestowing 3.5 times the risk of delivering before 34 weeks.

However, presenting at more than 30 weeks' gestation did not demonstrate elevated odds of delivering before 34 weeks or before 37 weeks, compared with presentation at 32 weeks' gestation.

Cervical dilatation—both on presentation and over the course of 6 hours following admission—was significantly predictive of preterm birth, even after controlling for multiple other variables such as maternal age, race, prenatal care, and gestational age on admission.

Each 1-cm increase in cervical dilatation on presentation more than doubled the odds of delivering before 37 weeks, a significant finding (*P* less than .0001). However, this risk was modified depending on obstetric history.

At a dilatation of 2 cm on admission, for example, the patients who were at highest risk of a preterm birth before 37 weeks were those with no previous births, followed by those with one or more prior preterm deliveries. Rates were lower for mothers who had a history of both preterm and full-term deliveries, and for those who previously had only had full-term deliveries.

The interaction between obstetric history and cervical dilatation was complex.

Patients with a previous preterm birth had the highest baseline risk of another preterm delivery before 37 weeks if cervical dilatation was not taken into consideration.

Within each obstetric history cohort, advancing cervical dilatation was significantly associated with preterm birth before 34 and 37 weeks. Advancing cervical dilatation had the greatest impact on patients with no prior preterm birth and the least impact on those with only a prior preterm birth.

Notably, more than 60% of women with a history of one or more full-term deliveries and no preterm deliveries carried their pregnancies beyond 34 weeks.

What happened after admission was also very relevant to the risk of preterm delivery.

Just 17.8% of the cohort (71 patients) de-



livered within 6 hours of admission.

Among the remaining 329 women, a 1-

to 2-cm change in cervical dilatation after admission conferred almost a three-fold risk of delivery before 34 weeks and a twofold risk of delivering before 37 weeks.

A 3-cm or greater change in cervical di-

latation was associated with a nearly 12fold increase in risk of a preterm birth before 34 weeks and a sevenfold increase in the odds of delivering before 37 weeks. All eight women with more than a 4-cm

Our goal is a trial examining

whether women with a low

managed without exposing

baseline risk can be

them to magnesium or

other tocolytics.

change in dilatation over the first 6 hours post admission delivered at fewer than 34

weeks.

The research pointed to a number of factors that should be considered in the management of women with

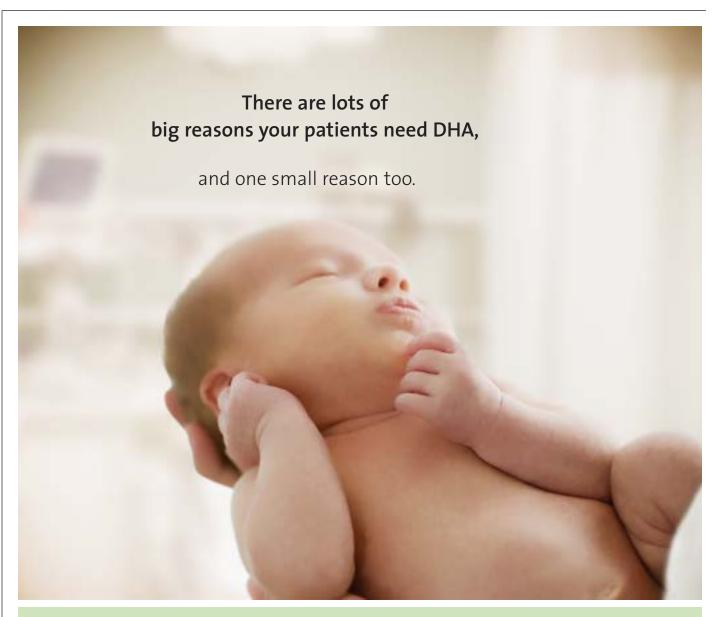
preterm labor, especially gestational age at presentation; cervical dilatation on presentation and cervical change over the 6

hours following admission; and obstetric history.

Further research is planned to randomize women with no previous preterm births and a low-risk cervical dilatation profile to tocolysis or expectant management.

"Our goal is to use this information to move into a trial that examines whether women with a low baseline risk can be managed without exposing them to magnesium or other tocolytics," she said.

Dr. Bastek's coresearchers included principal investigator Dr. Michal A. Elovitz, Dr. Sindhu Srinivas, and biostatistician Mary D. Sammel.



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\*Simopoulos, AP., Workshop on the essentiality of and recommended dietary intakes of omega-6 and omega-3 fatty acids. Ann Nutra Metab, 1999. 43 (2):127-30. ©2007 Martek Biosciences Corporation.

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