# Alter Pneumonia Strategies to Fight Resistance

## BY DIANA MAHONEY New England Bureau

MONTREAL — In vitro pneumococcal resistance continues to have a substantial role in guiding antibiotic choices and disease management plans for patients with community-acquired pneumonia, according to Michael S. Niederman, M.D.

Many surveillance studies have revealed an increasing global prevalence of in vitro drug resistance among pneumococcal isolates obtained from patients with community-acquired pneumonia. Updated treatment guidelines reflect these findings by stressing the need for clinicians to keep in mind local antibiotic resistance patterns as well as patient risk factors for infection with drug-resistant pathogens, Dr. Niederman said at the Second International Conference on Community Acquired Pneumonia

"Drug-resistant pneumococcus is more likely in certain at-risk populations, including people older than 65 years and those with immune suppression, exposure to a child in daycare, or a history of alcoholism, multiple medical comorbidities, or therapy with a  $\beta$ -lactam in the past 3 months," he said.

To minimize the opportunity for clinical failure of community-acquired pneumonia therapy related to antibiotic resistance, which can occur with any drug class, clinicians should be prepared to modify management approaches accord-

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llergic Reaction Dyspepsia Diarrhea Tooth Disorder Vomiting

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ingly, stressed Dr. Niederman of the State University of New York at Stony Brook. One such consideration is to use focused instead of broad-spectrum therapy as appropriate, he said.

'Broad-spectrum agents such as quinolones are frequently used in situations where they are both not indicated and unnecessary," he said. For example, in one study of 100 consecutive emergency department patients who were discharged on quinolone therapy, 81 of the patients

## Incidence Is Up For Some Strep Empyemas

SAN FRANCISCO — The incidence of pediatric pneumococcal parapneumonic empyema doubled in Utah and surrounding areas since introduction of the pneumococcal conjugate vaccine, Carrie L. Byington, M.D., said in a poster presentation at the annual meeting of the Infectious Diseases Society of America.

Activity of bacterial serotypes varies by geographical region. In the past decade, Utah has had one of the highest rates of pneumococcal parapneumonic empyema (PPE) in children due to Streptococcus pneumoniae serotype 1, which the vaccine does not cover, said Dr. Byington of the University of Utah, Salt Lake City, and associates.

A search of the Intermountain Health Care data warehouse found 776 cases of pediatric PPE between March 1996 and June 2005, 62% of which were treated at Primary Children's Medical Center, Salt Lake City. In the period 1996-2000, before introduction of 7-valent pneumococcal conjugate vaccine (Prevnar), the center saw 38 cases per year, compared with 72 cases annually between 2001 and 2004, a significant difference.

Among 295 cases of culture-confirmed invasive pneumococcal disease in children at the center, 74 were PPE, representing 18% of invasive pneumococcal disease in the prevaccine years and 32% since the vaccine.

The investigators retrieved and serotyped pleural and fluid isolates of S. pneumoniae from the 74 cases. The proportion of PPE due to serotypes covered in the vaccine decreased from 37% (9 of 24 cases) in the prevaccine era to 14% (7 of 50 cases) in more recent years.

Serotype 1 was the most common cause of PPE due to nonvaccine serotypes in both time periods, but disease due to other nonvaccine serotypes has become more common. Serotype 1 caused 11 (46%) of 24 PPE cases in the earlier period and 17 (34%) of 50 cases since the vaccine. Other nonvaccine serotypes caused only four cases (16%) of PPE in the prevaccine years but 26 cases (52%) of PPE in the postvaccine years.

The pneumococcal vaccine may need to be broadened to cover some of these serotypes, Dr. Byington suggested in an interview.

## **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)

(see DOSAGE AND ADMINISTRATION) WARNINGS BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagtis, and esophageal or gastric uicer (see PRECAUTIONS). PRECAUTIONS: General Mineral Metaolism: Hypocalcernia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA herapy. Adequate intake of calcium and vitamin D is important in all patients. Upper Gastrointestinal Effects: Bisphosphonates administered orally have been associated with dysphagia, esophagtis, and esophageal or gastric uicers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preaproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay patiential aritention 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 ecommended for use in patients with

We auve to compty 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 severe renal Impairment (creatinine clearance -30 mL/min). *Jaw Ostenorcosis*: Ostenorcosis, primarily in the jaw, has been reported in patients treated with bisphosphorates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmeropausal osteoporosis or other diagnoses. Known risk factors for osteonerorsis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids, ind co-mobil disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphorates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis a the jaw (0NJ) while on bisphosphorate treatment reduces the risk of OMJ. Clinical updrement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. *Musculoskeletal Pain:* In postmarkeline exuerience severe and escence

patient based on individual bénefit/risk assessment. Musculoskeldal Pain: In postmarketing experience, severe and occasionally incepacitating bone, joint, and/ or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of soleboprosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include BONIVA (Bandronate sodium) Tablets. Most of the patients were postmenopausal women. The line to onset of symptoms varied from one day to several months after starting the drug. Most patients had rechallenged with the same drug or another bisphosphonate. In placebo-controlled studies with BONIVA, the percentages of patients with these symptoms were similar in the BONIVA and placebo groups.

success wim success, the percentages of patients with these symptoms were similar in the BOINA and placebo groups. Information for Patients: Patients should be instructed to read the Patient information Leaflet carefully before taking BOINA, 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. -BOINA's hould 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 natacids, supplements or vitamins). -To facilitate delivery to the stomach, and thus reduce the potential for esophageal irration, BOINA's tablets should be swallowed whole with a full glass of plain water (6 to 8 a) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BOINA. -Plain water is the only drink that should be taken with BOINA. 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 oropharyngal ulceration. -The BOINA 150-mg tablet should be taken on the same date each month (ie, the patient's BOINA' day).

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If the once-monthly does is missed, and the patient's next scheduled BONWA day.
Is more than 7 days away, the patient should be instructed to take one BONWA 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient should then return to taking one BONWA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.
The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONWA day to take their tablet. The patient must wait until their next scheduled BONWA day to take their tablet. The patient must wait until their next scheduled BONWA day to take their tablet. The patient must wait until their next scheduled BONWA day to take their tablet. The patient should their eturn to taking one BONWA 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 delayed for at last of minutes following oral administration of BONWA in order to maximize absorption of BONWA.

absorption or 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.

new or worsening dysphagia, pain on swallowing, retrosternal pain, or hearburn. 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**). (see **PRECAUTIONS: Information for Patients**) (see **a**) (see Drug/Laboratory Test Interactions: Bisphosphonates are known to interfer with the use of bone-imaging agents. Specific studies with ibandronate have no been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by 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 5.2 ou or 40 mg/ko/daw 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 weter to NMRI mice (cumulative monthy exposure) and females up to 70 and 115 times, respectively, human 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 (220 to 400 times human exposure at the recommended dail oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown. *MuLagenesis*. There was no evidence for a mutagenic or clastogenic potential of samonella typhimurium and *Escherichia coli* (Ames test), mamalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human exposure at the recol were the set of whou male bernation test in human exposure dat a the table trans that a down. *MuLagenesis* there was no evidence for a mutagenic or clastogenic potential of samonella typhimurium and *Escherichia coli* (Ames test), mamalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation.

Balfionend upprintering and Escheriche Casy, maintenant cent mutagenesis assay in Chinese hamster V79 cells, and chronosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Imaniment of Fertility: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral does of 16 mg/kdyda (45 times human exposure at the recommended once-monthly oral does of 150 mg, based on AUC comparison). **Pregnancy:** *Pregnancy: Category C:* In female rats given oral does got 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation. 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 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 daily oral dose of 2.5 mg or 1 times human exposure at the recommended daily 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 oxe-monthly oral dose of 150 mg, based on AUC comparison) was likely related to maternal dystolac. In perinant 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 16 to besetting 4.6 times human exposure at the recommended daily oral dose of 2.5 mg 4.6 times human exposure at the recommended daily oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation itors was observed in rats treated from 14 days before mating through useration or during gestation, only at doses causing maternal dystola: and periparturient mortality, mer observed at doses 3.5 mg/kg/day (equivalent to human exposure at the recommended daily oral dose of 150 mg, based on AUC comparison). Periparturient mortality has also been observed with other

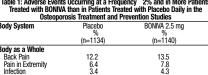
potential risk to the mother and fetus. Nursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast mikk actonentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk, because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman. Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

established. Gertatric 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 overal 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 Daily Dosing: Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal osteoporosis trials of us to 3 vears diration. The nueval advecement of the patients and to 3 vears diration.

using: using rearrent with oral BUNIVA 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 BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group and the placebo 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 liet adverse avents from the Treatment and Prevention Studies more daily

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 Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies Destrict Contents Destrict Con



Gastritis Metabolic and Nutritional Diso ders 4.2 4.8 Hypercholesterolemia usculoskeletal Syster 5.7 3.6 3.2 5.1 3.3 2.7 wyaigia Joint Disorder Arthritio 5.8 2.6 2.5 1.9 6.5 3.7 3.0 2.2 Vertigo Nerve Root Lesion 33.7 10.0 5.9 2.5 33.2 6.8 4.3 1.5 Pharyngitis rogenital System Urinary Tract Infection 4.2 5.5 
 Urinary Tract Infection
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 Once-Monthly Dosing:
 In a 1-year, double-blind, multicenter study comparing BONWA 2.5 mg once daily and BONWA 150 mg once monthly in women with 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 BONWA 150 mg once-monthly group. The percentage of patients who withchew from treatment due to adverse events was approximately 8.9% in the BONWA 2.5 mg daily group and 7.8% in the BONWA 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 an Incidence of at Least 2% in Patients Treated with BONWA 150 mg Once Monthly or 2.5 mg Daily

 Body System/Adverse Event 2.5 mg daily
 BONWA BONWA
 2.5 mg daily 150 mg monthly (n=396) (n=395) Vascular Disorders Hypertension Gastrointestinal Disorders 7.3 6.3 5.6 5.1 5.1 4.0 7.8 tal and Con thralgia ack Pain ain in Extremity ocalized Osteoarthritis 5.6 4.5 4.0 3.0 2.0 1.8 Myalgia Muscle Cramp 0.8 2.0 3.8 4.3 3.5 4.0 3.5 2.5 asopharyngitis bronchilis Urinary Tract Infection Upper Respiratory Tract Infection **Jervous System Disorders** Headache Dizziness **Jeneral Disorders** 1.8 2.3 2.0 4.1 1.0 3.3 2.3 3.3 Skin and Subcutaneous Tissue Disorders 2.3 Rash<sup>e</sup> Psychiatric Disorders 0.8 2.0 Combination of abdominal pain and abdominal pain upper Combination of influenza-like illness and acute phase reaction Combination of rash pruritic, rash macular, rash papular, rash o erythematous, dermatitis, dermatitis allergic, dermatitis medicame and exember

erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem Patientis with a previous history of gastointestinal disease, including patients with peptic ulcer without recent bleeding or hospitalization and patients with dyspepsia 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 moce-monthly regimen compared to the 2.5 mg once-daily regimen. **Ocular Adverse Events:** Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveits and scientis. 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 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 study with BONIVA 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatamia. Similarly, no changes were noted for the 150 mg once-monthly administration in the 1-year study. **OVERDOSAGE:** to specific information is available on the treatment of overdosage

were noted for the 150 mg once-monthly administration in the 1-year's study. **OVERDOSAGE**: No specific information is available on the treatment of overdosage with BONNA: However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointsstina diverse vertex stomach, dyspensia, esophaglits, gastrits, or uicer. Milk or antacids should be given to bind BONNA. Due to the risk of esophage irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

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-Sherry Boschert

had inappropriate indications for the drug, and of the 19 in whom quinolone therapy was appropriate, only 1 was given the correct dose for the correct duration, he said (Arch. Intern. Med. 2003;163:601-5).

"This is the type of behavior that drives more resistance and has to be avoided," Dr. Niederman added.

Because recent prior therapy with  $\beta$ -lactams, macrolides, or quinolones predicts subsequent pneumococcal resistance to the agent that was used, "it is imperative that clinicians take a history of recent antibiotic usage and be prepared to choose an agent that differs from what was used previously," Dr. Niederman said. "This

form of patient-specific antibiotic rotation only works if we have choices, which requires an understanding of the acceptable options for therapy."

For example, studies have shown that penicillin resistance probably has therapeutic significance only when MIC values are at least 4 mg/L.

"If  $\beta$ -lactam resistant pneumococcus is suspected, ceftriaxone [Rocephin] may be a reliable choice, while the cephalosporin cefuroxime [Ceftin] may be associated with increased mortality if used in the presence of in vitro resistance to this agent," he said.

In general, when managing patients at

risk for drug resistance, "clinicians should choose a highly active antipneumococcal agent to minimize selection pressure for more organisms emerging with higher levels of resistance," Dr. Niederman said.

Patients not likely to have resistance should receive focused therapy with macrolides or ketolides, "reserving more potent agents for the appropriate setting," he added.

Ketolide use in particular "can improve the management of community acquired pneumonia in this era of pneumococcal antibiotic resistance by adding another choice to the heterogeneity of options," he said. Studies have shown that telithromycin (Ketek)—the first ketolide available for clinical use—is an effective outpatient treatment for mild to moderate community-acquired pneumonia, even in older patients, those with higher pneumonia severity index scores, and those with bacteremia.

"The agent's rapid bactericidal effects appear to make short treatment durations feasible, and its mechanisms of action may avoid the induction of resistance, while maintaining good intrinsic activity against pneumococci, including those that are macrolide resistant," Dr. Niederman said.

## Moxifloxacin Treats Aspiration Pneumonia

MONTREAL — The potent respiratory fluoroquinolone moxifloxacin is as safe and effective as combination ampicillin/sulbactam therapy for the treatment of aspiration-associated pulmonary infections, Sebastian Ott, M.D., reported in a poster presentation at an international conference on community-acquired pneumonia.

To compare the efficacy, safety, and tolerability of moxifloxacin (Avelox) with that of ampicillin/sulbactam (Unasyn) for the treatment of aspiration pneumonia and primary lung abscess, Dr. Ott of the Helios Chest Hospital Heckeshorn in Berlin and his colleagues enrolled 139 patients diagnosed with either condition in a multicenter, open-label trial.

Nearly 65% of the patients in the study were diagnosed solely with aspiration pneumonia, and definite or presumptive pathogens were isolated in 45 subjects, he said.

Of the 139 patients, 96 were treated according to protocol: 48 were randomized to receive 400 mg of moxifloxacin given intravenously once daily followed by oral moxifloxacin for 7-14 days or until complete resolution of radiologic and clinical signs of infection, and 48 received 1.5-3.0 g of ampicillin/sulbactam intravenously twice daily followed by oral administration for the same duration.

At the end of treatment, the overall clinical response rate for both groups was 67%. In the moxifloxacin group, 59% of patients with aspiration pneumonia and 80% of those with primary lung abscess had responded to the antibiotic treatment.

Among those who received ampicillin/sulbactam, 64% of the aspiration pneumonia patients and 82% of the primary lung abscess patients responded to treatment.

Both of the regimens were well tolerated to a similar degree, "even after longterm administration," Dr. Ott said. "The benefit of moxifloxacin is that its [oncedaily] dosing is more convenient."

The findings of this study provide clinicians with an important therapeutic option to add to their toolbox for treating aspiration-related pulmonary infections, which are rare but potentially life threatening.

—Diana Mahoney

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\* Pharmacokinetic data. Megace ES 625 mg/5 mL and megestrol acetate oral suspension 800mg/20 mL are bioequivalent in the fed condition.<sup>2</sup>

### **Important Safety Information**

Megace ES and megestrol acetate oral suspension are contraindicated in patients with a history of hypersensitivity to megestrol acetate or any component of the formulation, or patients with known or suspected pregnancy. Evidence of adrenal suppression has been observed in patients receiving megestrol acetate oral suspension. The glucocorticoid activity of megestrol acetate oral suspension has not been fully evaluated. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's Syndrome have been reported in association with the chronic use of megestrol acetate. The most common adverse events ( $\geq$ 1% and > placebo) associated with Megace ES 625 mg/5 mL and megestrol acetate oral suspension 800 mg/20 mL are impotence, flatulence, rash, hypertension, fever, decreased libido, insomnia, dyspepsia, and hyperglycemia. Women who participated in studies reported breakthrough bleeding; however, it is unknown if these events are drug- or disease-related.

References: 1. Megace ES Prescribing Information. Par Pharmaceutical Companies, Inc. 2005. 2. Data on file. Par Pharmaceutical Companies, Inc. 3. NanoCrystal<sup>®</sup> Technology Group. Technology Focus: Meeting the Challenges of Drug Delivery Brochure. Elan Drug Delivery, Inc. King of Prussia, PA 2005.

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