

New Tools Help Doctors Address HIV Prevention

BY SHERRY BOSCHERT
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SAN FRANCISCO — The Centers for Disease Control and Prevention will offer new tools early next year for health care providers who treat patients with HIV to improve prevention of viral transmission.

Of the approximately 40,000 new HIV infections in the United States each year, about a third are transmitted by people who know that they're infected with HIV.

To make a dent in these numbers, physicians must get more comfortable asking detailed questions about sexual practices, drug use, and other sensitive topics and must learn to deliver brief HIV prevention messages at every visit with HIV-positive patients, a panel of experts agreed at the annual meeting of the Infectious Diseases Society of America.

If you're not comfortable questioning and talking in a nonjudgmental fashion with a patient who mentions having a

"booty bump" for sex, for example (that's sex with an amphetamine enema), the new Prevention in Care materials might help, said Mark W. Thrun, M.D., medical director of HIV prevention at the Denver Department of Public Health STD/HIV Prevention Training Center.

Physicians who ask HIV-positive patients about aspects of transmission prevention will find that 80% are doing what they need to do to keep themselves and others safe.

The campaign aims to help manage the other 20% by offering free printed materials in English and Spanish available in early 2006 at www.cdcnpin.org or by emailing info@cdcnpin.org. Key materials include a resource kit with a questionnaire, sample prevention messages, and tips to help simplify discussions with patients. Posters and handouts provide graphic displays of the relative risks of HIV transmission from various sexual activities with or without a condom, and illustrate that HIV transmission can happen even with a low viral load.

The CDC, in conjunction with other federal agencies, also is planning training sessions at dozens of medical clinics to get physicians to use evidence-based interventions for HIV prevention. A prospective, randomized study of 585 HIV-positive

MEGACEES[®] 625 mg/5 mL oral suspension

megestrol acetate

RX ONLY

Brief summary: For complete details, please see full Prescribing Information for Megace[®] ES.

INDICATIONS AND USAGE

Megace[®] ES (megestrol acetate) oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. Known or suspected pregnancy.

WARNINGS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, (see **PRECAUTIONS: Impairment of Fertility** section). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Megestrol acetate is not intended for prophylactic use to avoid weight loss. (See also **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility** section.)

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. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic Megace[®] ES therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (e.g., hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic Megace[®] ES therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid during stress or serious intercurrent illness (e.g., surgery, infection).

PRECAUTIONS

General

Therapy with Megace[®] ES (megestrol acetate) oral suspension for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric diseases.

Effects on HIV viral replication have not been determined.

Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics

Exacerbation of pre-existing diabetes with increased insulin requirements have been reported in association with the use of megestrol acetate.

Information for Patients

Patients using Megace[®] ES (megestrol acetate) should receive the following instructions:

- This medication is to be used as directed by the physician.
- Megace[®] ES (625 mg/5 mL) does not contain the same amount of megestrol acetate as Megace[®] oral suspension or any of the other megestrol acetate oral suspensions. Megace[®] ES contains 625 mg of megestrol acetate per 5 mL whereas Megace[®] oral suspension and other megestrol acetate oral suspensions contain 800 mg per 20 mL.
- The prescriber should inform the patient about the product differences to avoid overdosing or underdosing of megestrol acetate. The recommended adult dosage of Megace[®] ES is one teaspoon (5 mL) once a day. Please see table in **DOSAGE AND ADMINISTRATION** section.
- Report any adverse reaction experiences while taking this medication.
- Use contraception while taking this medication if you are a woman capable of becoming pregnant.

- Notify your physician if you become pregnant while taking this medication.

Drug Interactions

Pharmacokinetic studies show that there are no significant alterations in pharmacokinetic parameters of zidovudine or ribavirin to warrant dosage adjustment when megestrol acetate is administered with these drugs. A pharmacokinetic study demonstrated that coadministration of megestrol acetate and indinavir results in a significant decrease in the pharmacokinetic parameters (~36% for C_{max} and ~28% for AUC) of indinavir. Administration of a higher dose of indinavir should be considered when coadministering with megestrol acetate. The effects of indinavir, zidovudine or ribavirin on the pharmacokinetics of megestrol acetate were not studied.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times lower than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing Megace[®] ES (megestrol acetate) oral suspension and in surveillance of patients on therapy. (See **WARNINGS** section.)

Mutagenesis

No mutagenesis data are currently available.

Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05 to 12.5 mg/kg) less than that indicated for humans (13.3 mg/kg); in these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

Pregnancy

Pregnancy Category X. (See **WARNINGS** and **PRECAUTIONS: Impairment of Fertility** sections.) No adequate animal teratology information is available at clinically relevant doses.

Nursing Mothers

Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megace[®] ES (megestrol acetate) oral suspension is required.

Use in HIV Infected Women

Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited.

All 10 women in the clinical trials reported breakthrough bleeding.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of megestrol acetate oral suspension in the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with AIDS did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Megestrol acetate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Clinical Adverse Events

Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial are listed below by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing Megace[®] ES (megestrol acetate) oral suspension.

Adverse events which occurred in 1% to 3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than

	ADVERSE EVENTS % of Patients Reporting												
	Trial 1 (N=236)				Trial 2 (N=87)				Open Label Trial				
Megestrol Acetate, mg/day No. of Patients	Placebo N=34	100 N=68	400 N=69	800 N=65	Placebo N=38	800 N=49	1200 N=176						
Diarrhea	15	13	8	15	8	6	10						
Impotence	3	4	6	14	0	4	7						
Rash	9	9	4	12	3	2	6						
Flatulence	9	0	1	9	3	10	6						
Hypertension	0	0	0	8	0	0	4						
Asthenia	3	2	3	6	8	4	5						
Insomnia	0	3	4	6	0	0	1						
Nausea	9	4	0	5	3	4	5						
Anemia	6	3	3	5	0	0	0						
Fever	3	6	4	5	3	2	1						
Libido Decreased	3	4	0	5	0	2	1						
Dyspepsia	0	0	3	3	5	4	2						
Hyperglycemia	3	0	6	3	0	0	3						
Headache	6	10	1	3	3	0	3						
Pain	6	0	0	2	5	6	4						
Vomiting	9	3	0	2	3	6	4						
Pneumonia	6	2	0	2	3	0	1						
Urinary Frequency	0	0	1	2	5	2	1						

1% are not included. There were no significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole - abdominal pain, chest pain, infection, moniliasis and sarcoma; **Cardiovascular System** - cardiomyopathy and palpitation; **Digestive System** - constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis; **Hemic and Lymphatic System** - leukopenia; **Metabolic and Nutritional** - LDH increased, edema and peripheral edema; **Nervous System** - paresthesia, confusion, convulsion, depression, neuropathy, hyposthesia and abnormal thinking; **Respiratory System** - dyspnea, cough, pharyngitis and lung disorder; **Skin and Appendages** - alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder; **Special Senses** - amblyopia; **Urogenital System** - albuminuria, urinary incontinence, urinary tract infection and ureinostomiasis

Postmarketing

Postmarketing reports associated with megestrol acetate oral suspension include thromboembolic phenomena including thrombophlebitis and pulmonary embolism and glucose intolerance (see **WARNINGS** and **PRECAUTIONS** sections).

OVERDOSAGE

No serious unexpected side effects have resulted from studies involving megestrol acetate oral suspension administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability; however, due to its low

PRODUCT DIFFERENCES		
	Megace [®] ES Oral Suspension	Megace [®] and other megestrol acetate oral suspensions
mg/mL	125 mg/mL	40 mg/mL
Recommended Daily Dose	625 mg	800 mg
Daily Volume Intake	5 mL (teaspoon)	20 mL (dosing cup)
Formulation	Concentrated formula	Regular Formula

solubility it is postulated that dialysis would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION

The recommended adult initial dosage of Megace[®] ES (megestrol acetate) oral suspension is 625 mg/day (5 mL/day or one teaspoon daily). Please refer to the table below for correct dosing and administration. Shake container well before using.

In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day of megestrol acetate oral suspension (800 mg/20 mL equivalent to 625 mg/5 mL of Megace[®] ES formula) were found to be clinically effective.

SPECIAL HANDLING

Health Hazard Data

There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

Exposure or overdose at levels approaching recommended dosing levels could result in side effects described above (see **WARNINGS** and **ADVERSE REACTIONS** sections). Women at risk of pregnancy should avoid such exposure.

Manufactured by:

PAR PHARMACEUTICAL, INC.

Spring Valley, NY 10977

www.MegaceES.com

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Sex, culture, gender, and socioeconomic factors can all get in the way of prevention.

DR. NEWMAN

patients found that brief, safer-sex counseling emphasizing the negative consequences of unsafe sex reduced instances of unprotected anal or vaginal intercourse by 38% among patients with two or more sex partners (AIDS 2004;18:1179-86).

Sex isn't the only topic that can get in the way of delivering prevention messages, said panelist Meg D. Newman, M.D., an HIV specialist at San Francisco General Hospital. Racial and ethnic minorities and women make up an increasing proportion of new HIV infections. Cultural issues, gender differences, and socioeconomic factors play roles in patients' decision-making and their openness to prevention messages, she said.

Behavioral change is not always a linear process, she added. "Prevention for positives is about meeting someone where they are and helping them move to a greater knowledge, greater self-acceptance, and self-respect," Dr. Newman said.

Never assume that your patients have had HIV education, said panelist Jesse Milan Jr., J.D., who has HIV. Giving them one lesson is not enough. Remind them about prevention every time you see them, said Mr. Milan of Silver Spring, Md.

Ask patients probing questions about their behavior and knowledge of HIV transmission, he said. "If you don't ask, they won't tell," he said.

Dr. Thrun compiled results of separate studies in 1999, 2003, and 2004 showing that far too many physicians don't assess risks for sexually transmitted diseases (STDs). Approximately 55% of 208 primary care providers assessed STD risk in one study, and routine STD assessment was reported by only around 35% of 3 million private physicians, 18% of 315 physicians not trained in infectious diseases, 10% of 315 physicians with infectious diseases training, and 15% of 417 HIV care providers.