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DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

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Pharmacists make no bones about treating, preventing osteoporosis

It's preventable and 28 million people need your help

Osteoporosis is largely a preventable disease. Its prevention, however, requires proactive efforts and education. Pharmacists are well-equipped to provide the necessary education and help people take those prophylactic steps.

Osteoporosis is not limited to elderly people. If prophylactic steps are not taken early in life, bone loss will occur early. According to the National Osteoporosis Foundation (NOF), 10 million Americans have osteoporosis, and 18 million more have low bone mass, which puts them at increased risk of osteoporosis. That's 28 million Americans affected by osteoporosis. Unless awareness of the disease is raised and preventive measures taken, that number is expected to increase to 41 million Americans affected by 2015.[1]

Osteoporosis itself is not life-threatening. It progresses without symptoms, characterized by bone loss and deterioration of the skeleton.

"However, osteoporosis leads to fractures, especially of the hip, spine, wrist, and ribs," says **Lynn Chard-Petrinjak**, NOF communications coordinator.

"The mortality rate is high in elderly suffering from hip fracture," Chard-Petrinjak tells *Drug Utilization Review*. In fact, a staggering 24% of hip-fracture patients who are 50 years and older die in the year following their fracture, according to the NOF.

Furthermore, the rate of

Executive Summary

Pharmacists can play a critical role in osteoporosis prevention by educating patients. Action items include the following:

- ☐ Raise level of awareness of osteoporosis:
  - — Discuss high incidence and cost for a preventable disease.
- ☐ Educate patients:
  - — prevention;
  - — screening;
  - — drug therapy.
- ☐ Make sure all at-risk patients are on calcium supplements with vitamin D:
  - — Intervene with medical staff on behalf of patients.
  - — Watch for indications of osteoporosis risk and help medical teams communicate across disciplines.

hip fracture is two to three times greater in women than in men, but twice as many men die in the year following hip fracture as women.

According to the NOF, while women are four times more likely than men to develop the disease, men also suffer from osteoporosis. One-fourth of those who were ambulatory prior to the fracture require long-term care afterward.

Although everyone loses some bone with age, the stooped posture of kyphosis and a loss of height greater than one to two inches are caused by vertebral fractures due to osteoporosis.

A study performed by Friedman and published last year in the *Journal of Bone and Joint Surgery* shows that fewer than one-fourth of women older than 55 with risk factors for osteoporosis are screened for osteoporosis or are followed up with drug therapy, according to Chard-Petrinjak.

"Osteoporosis is responsible for 250,000 wrist fractures per year," she says. "Nontraumatic wrist fracture is often the first indication of osteoporosis. There are no overt symptoms until a bone is broken."

Patients need to be made aware of the effects that corticosteroids, some cancer medications, and other medications and diseases have on bones. "Pharmacists who dispense medication for the pain associated with bone fractures can help lead patients to ask their physicians about the need for screening and treatment of osteoporosis."

The importance of being screened

"Low bone mineral density and existing fractures are the two greatest risk factors for fractures," says **Kelly Reith**, senior marketing communications specialist at Hologic Inc., in Bedford, MA, manufacturer of bone densitometry, mammography, and general radiography systems. "We have technology that allows physicians to look for vertebral fractures. With the same instrument used to determine bone density, we can generate an image of the spine to find and assess fractures. This leads to better determination of fracture risk."

According to the NOF, bone density tests can measure bone density at various sites of the body and can:

- detect osteoporosis before a fracture occurs;
- predict the probability of future fractures;
- determine the rate of bone loss or monitor the effects of drug therapy when the test is performed at intervals of one year or more.

"The gold standard in determining bone mineral density is dual X-ray absorptiometry, or DXA," says Reith. "DXA provides an accurate measure of BMD and sensitive measures of bone loss or gain over time."

Third-party payers will reimburse for DXA tests in many situations, she says. Through the efforts of the NOF, Medicare now covers bone-density tests for those who are at risk of osteoporosis. Coverage remains to be standardized for both men and women under age 65.

The National Osteoporosis Foundation has published physician guidelines for the diagnosis and treatment of osteoporosis. Patients who should be screened include:

- women older than 65;
- postmenopausal women younger than 65 with one or more risk factors (not including being postmenopausal);
- those on high-dose corticosteroids;
- those on an approved therapy for treatment of osteoporosis, in order to monitor for patient response to treatment;
- those with a family history of osteoporosis (with a first-degree relative);
- those with a personal history of fracture.

There are no guidelines specific to men, according to Chard-Petrinjak. "However, some of the same principles for screening would apply, such as men who are on steroid therapy and those suffering nontraumatic fractures as adults."

Beyond these conditions for screening in men, there is a question about whether third-party payers reimburse for the tests.

"Patients and friends who fit into any of these categories for screening but who are not screened, should be encouraged to ask their physicians to order the appropriate test for them." Osteoporosis doesn't fall under any one particular specialty. Many physicians treat

COMING IN FUTURE MONTHS

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- Pharmacists in prevention and treatment of stroke
- Evaluating evidence-based medicine
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patients for osteoporosis, including endocrinologists, gerontologists, and generalists, according to Chard-Petrinjak. By inquiring about the screening history of patients, pharmacists can help patients get a jump on osteoporosis treatment.

Lack of awareness requires education

Despite educational efforts from the NOF and others, lack of awareness remains a problem, according to Reith — and not only among patients.

"Health care providers are also sometimes unaware," she says. Occasionally, patients are hospitalized because of hip fractures, yet are discharged without ever being assessed or counseled for osteoporosis," she says. Patients may undergo orthopedic surgery and fail to question whether osteoporosis played a role in their fracture. Better communication across disciplines can help improve diagnosis.

Osteoporosis causes more than 1.5 million fractures each year including:

- ***300,000 hip fractures;***
- ***700,000 vertebral fractures;***
- ***250,000 wrist fractures;***
- ***300,000 other fractures.[1]***

Where one link in the health care chain fails to question or be educated, another link must be strong. "Pharmacists are in the perfect position to step in on the patient's behalf in this kind of scenario," says Reith. "Pharmacists who are attentive to the patient's full drug regimen as it relates to disease states can intervene and query physicians about the potential need for osteoporosis assessment and treatment."

"Pharmacists are an important part of the education process," Reith says. "Their role in today's medicine is a lot more than distributive. They can do a lot toward teaching patients about both the prevention and treatment of osteoporosis. Educating about the risk factors to watch for helps raise awareness. Low bone mineral density is a primary risk factor and evidence has established that existing fracture is another."

Other risk factors for osteoporosis include:

- a family history of osteoporosis;
- female sex;
- thinness or a small frame;
- advanced age;
- menopause, including early or surgically induced menopause;
- abnormal absence of menstrual periods (amenorrhea);
- anorexia nervosa or bulimia;
- diet low in calcium;
- use of medications including corticosteroids and anticonvulsants;
- low testosterone levels in men;
- sedentary lifestyle;
- cigarette smoking;
- excessive use of alcohol;
- Caucasian or Asian race, although African-Americans and Hispanic-Americans are also at significant risk.[1]

The role of pharmacists is especially important for patients on high-dose corticosteroids, according to Reith. "These patients often get overlooked as being at risk for osteoporosis," she says. "You can have a young person on steroids with bone loss, who is at risk of fracture. Osteoporosis therapy can prevent such bone loss. Too often, patients initiating short-term treatment end up on long-term therapy with steroids and are at high risk of bone loss and subsequent fracture."

One step pharmacies can take in preventing osteoporosis in this patient population, according to Reith, is to flag high-dose steroids in the pharmacy computer so that pharmacists will check the patient profile for drugs to counter bone loss. In the absence of any such drugs, the pharmacist should follow up with a note to or conversation with the patient's physician about treatment, or at least an assessment, for osteoporosis.

Augment teaching with brochures

Several brochures are available for health care providers and for patients through the NOF Web site at www.nof.org. Some might serve to augment inservices that pharmacists perform for house staff. They would make good giveaways to patients as they are discharged from the hospital following hip surgery. In addition, you can subscribe to the NOF newsletter by e-mail.

The estimated national expenditures to hospitals and nursing homes for osteoporotic and associated fractures was $13.8 billion in 1995, representing $38 million each day, and the cost is rising. If nothing is done to reduce the incidence of osteoporosis, the cost of the disease will be an estimated $60 billion by the year 2020.[1]

"Primary prevention is extremely important,"

Reith says. "The No. 1 population where we make a difference is with young girls. If we can make sure they have a good supply of calcium in their diet, their peak bone density will be high. The peak is all you get," says Reith. "The higher the peak, the better head start you have for the rest of your life."

By around 20 years old, most women have acquired 98% of their total skeletal mass. Building strong bones during the early years, then, can be the strongest defense against development of osteoporosis later in life. Bone loss begins around age 30. The decline is gradual at first for both men and women. Once women hit menopause, though, their decline accelerates significantly, while that of men continues its gradual decline.

Components of a program to help prevent osteoporosis include:

- a balanced diet rich in calcium and vitamin D;
- weight-bearing exercise;
- a healthy lifestyle with no smoking and limited alcohol intake;
- bone density testing and medication when appropriate.

Prevention and treatment — but no cure

Prevention of osteoporosis is important because, while there are treatments for osteoporosis, currently there is no cure. Prevention is important throughout life, but the steps listed above may not be sufficient once a woman goes through menopause. Estrogen replacement therapy or other drug therapy for osteoporosis may be required to help protect against bone loss. A woman may lose as much as 20% of bone mass in the first five to seven years after menopause. Many physicians recommend hormone replacement therapy (HRT) in postmenopausal patients no matter what the woman's bone density because of its potential cardioprotective effects.

"Calcium and vitamin D alone are not enough," Reith continues. "Some might believe that calcium with D constitutes treatment. They're not. Calcium and vitamin D are an important part of any good diet, whether or not you have osteoporosis. They should be part of your diet and part of any prevention measure, in addition to whatever the physician may prescribe on top of that."

Reith refers to a recent study by Robert Lindsay and colleagues, published in the Jan. 17, 2001, issue of the *Journal of the American Medical Association*.[2] In this study, 2,725 postmenopausal women randomized to placebo in previous osteoporosis trials were evaluated. In the previous studies, all of the women had received calcium supplementation (1,000 mg/d) and vitamin D supplementation if their serum levels were low). Lindsay found that, within the first year following a vertebral fracture, one in five women will suffer another fracture. The results of this study point to the great need for identification of osteoporosis and intervention in these patients. "It can be a downhill cascade of events with osteoporosis," says Reith.

Although pharmacists are fully capable of educating patients about disease states, risk factors, and prevention, drug information is their specialty. "This is an area that patients need a lot of help with for both information and compliance," notes Reith.

According to NOF, national nutrition surveys show that many women and young girls consume less than half the amount of calcium recommended to grow and maintain healthy bones. Depending a person's your age, an appropriate calcium intake falls between 1,000 and 1,300 mg a day. If a patient gets inadequate amounts of calcium through normal dietary habits, a calcium supplement can help compensate.

Patients who take calcium supplements must know that calcium needs vitamin D for proper absorption. Without adequate vitamin D, the body is unable to absorb calcium from foods and resorts to taking calcium from the bones. Vitamin D is available from two natural sources: through the skin following exposure to sunlight and through the diet. The recommended daily intake of vitamin D is 400 to 800 IU per day. Those with inadequate natural sources of vitamin D must take supplemental D or ingest fortified dairy products, egg yolks, saltwater fish, or liver.[1]

Many patients aren't aware of all the potential benefits of HRT. Pharmacists can provide the necessary patient education. Counseling about potential side effects also fills an important gap, because a large percentage of women who start HRT discontinue it due to real or perceived side effects. Many women on HRT don't realize their bones are benefitting from the therapy. Better knowledge of the benefits of therapy may lead to better patient compliance.

Although there is no cure for osteoporosis, there are steps that can be taken to prevent it or to retard its progress. The following medications

are approved by the FDA for use in postmenopausal women for the prevention and/or treatment of osteoporosis.[1]

• **Estrogens:** Estrogen replacement therapy (ERT) is approved for the prevention and management of osteoporosis. This therapy reduces bone loss, increases bone density in both the spine and hip, and reduces the risk of hip and spinal fractures in postmenopausal women. ERT is available both in pill form and as a patch. This therapy is effective even when started in patients older than 70. Estrogen taken alone can increase the risk of endometrial cancer. To eliminate this risk, progestin is combined with the estrogen (HRT) for women with an intact uterus. ERT/HRT relieves symptoms associated with menopause and has shown beneficial effects on both bone and cardiovascular health. Side effects may include nausea, bloating, breast tenderness, hypertension, and formation of blood clots. Studies on the relationship between estrogen and breast cancer risk have been inconclusive.

'The No. 1 population where we make a difference is with young girls. If we can make sure they have a good supply of calcium in their diet, their peak bone density will be high.'

• **Alendronate (Fosamax):** a bisphosphonate approved for the prevention and treatment of postmenopausal osteoporosis, treatment of male osteoporosis, and treatment of glucocorticoid-induced osteoporosis in men and women. In October 2000, the FDA approved two dosage strengths of alendronate for once-weekly dosing. The 70 mg dose was approved for the treatment of postmenopausal osteoporosis, the 35 mg dose for the prevention of postmenopausal osteoporosis.

"Once-weekly dosing may help increase patient compliance," says Reith. In postmenopausal women with osteoporosis, alendronate reduces bone loss, increases bone density in both the spine and hip, and reduces the risk of fractures of both the spine and hip. Side effects are uncommon but can include abdominal or musculoskeletal pain, nausea, heartburn, or esophageal irritation. Like all bisphosphonates, alendronate must be taken on an empty stomach. It is best taken with a full glass of water first thing in the morning, followed by at least a half-hour wait until the first food, beverage, or medication of the day. To minimize side effects, patients must remain in an upright position for at least half an hour after taking the drug.

"One could argue that bisphosphonates reverse or prevent the process because they build or maintain bone mineral density," Reith adds. Focusing on the consequence of osteoporosis — fracture — bisphosphonates are the only drugs proven in double-blind clinical trials to reduce vertebral fractures, nonvertebral fractures as a whole, and hip fractures."

• **Calcitonin (Miacalcin):** approved for treatment of postmenopausal osteoporosis only. Calcitonin is a hormone that occurs naturally and is involved in calcium regulation and bone metabolism. In women who are at least five years beyond menopause, calcitonin slows bone loss, increases spinal bone density, and, according to anecdotal reports, relieves the pain associated with bone fractures. Calcitonin reduces the risk of spinal fractures but does not appear to have a significant effect on non-vertebral fractures. Studies on fracture reduction are ongoing. Because calcitonin is a protein, it cannot be taken orally (it would be digested before it could be effective). Calcitonin is available as an injection or a nasal spray. While it does not affect other organs or systems in the body, injectable calcitonin may cause an allergic reaction and unpleasant side effects such as flushing of the face and hands, urinary frequency, nausea, and a skin rash. The only side effect reported with nasal calcitonin is rhinorrhea.

• **Raloxifene (Evista):** approved for the prevention and treatment of postmenopausal osteoporosis. Raloxifene is classified a selective estrogen receptor modulator (SERM) and appears to prevent bone loss at the spine, hip, and body. It also produces small increases in bone mass. After three years of use, raloxifene reduces the risk of spine fractures by about 50%. Like estrogens, SERMs produce changes in blood lipids that may protect against heart disease, although the effects are not as potent as those of estrogen. Unlike estrogens, SERMs do not appear to stimulate uterine or breast tissue. While side effects are not common, those reported include hot flashes and deep vein thrombosis, the latter of which is also associated with estrogen therapy. Research on raloxifene is ongoing.

• **Risedronate (Actonel):** a bisphosphonate approved for prevention and treatment of postmenopausal osteoporosis and for the prevention

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and treatment of glucocorticoid-induced osteoporosis in men and women. A daily dose of 5 mg slows bone loss, increases bone density, and reduces the risk of spine and non-spine fractures. As with alendronate, risedronate must be taken on an empty stomach, first thing upon rising in the morning, with a glass of plain water. Patients should remain upright for at least a half hour following the dose and refrain from eating, drinking, or taking other medications during that time. Side effects including stomach upset, constipation, diarrhea, bloating, gas, or headache were reported for risedronate with similar incidence as with placebo.

• **Other therapies** under investigation include sodium fluoride, vitamin D metabolites, parathyroid hormone, other bisphosphonates, and other SERMs.

Pharmacists know that compliance is a significant issue with HRT. Anything pharmacists can do to promote patient compliance will potentially help in the fight against bone loss. With bisphosphonates, patients have to take them correctly for proper absorption and to avoid potential side effects.

"The more pharmacists educate their patients — both those at risk for osteoporosis and those undergoing treatment — the more patients will benefit," Reith says.

References

1. National Osteoporosis Foundation. Web site: www.nof.org.

2. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285:320-3. ■

Educate patients about Accutane-suicide link

Although it's often difficult to prove that a drug is the direct cause of a side effect, many pharmacists prefer to err on the side of caution and assume that the cause-and-effect relationship exists.

That's the case with isotretinoin (Accutane) and its potential link to depression and suicide, as explained in a recent letter from **Janet Woodcock**, MD, director of the Center for Drug Evaluation and Research. As Woodcock's letter points out, "When there is reasonable suspicion of an association, patients should be informed." (Read the full letter at www.fda.gov/cder/drug/infopage/accutane/default.htm.)

Pharmacists can help confirm patient understanding of all aspects of isotretinoin use when they counsel patients at the time of dispensing the drug. A revised informed consent form has been created for patients and parents or guardians of patients younger than 18 prior to the beginning of treatment with isotretinoin. The consent form addresses the possible link between the drug and depression or suicide. Included in the consent form is the following language:

• I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane. Some people have had other signs of depression while taking Accutane (see below).

• Before I start taking Accutane, I agree to tell my health care provider if, to the best of my knowledge, I have ever had symptoms of depression (see below), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

• Before I start taking Accutane, I agree to tell my health care provider if, to the best of my knowledge, anyone in my family has ever had

symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.

• Once I start taking Accutane, I agree to stop using Accutane and tell my provider right away if any of the following happen. I:

— start to feel sad or have crying spells;
— lose interest in my usual activities;
— have changes in my normal sleep patterns;
— become more irritable than usual;
— lose my appetite;
— become unusually tired;
— have trouble concentrating;
— withdraw from family and friends;
— start having thoughts about hurting yourself / myself or taking your / my own life (suicidal thoughts). ■

Antiretrovirals in pregnant patients warrant caution

Three cases of fatal lactic acidosis have been reported in pregnant women treated throughout pregnancy with the combination of stavudine (Zerit) and didanosine (Videx). Based on these cases, Bristol-Myers Squibb (BMS) asks that caution be used when combining stavudine and didanosine during pregnancy. The combination is recommended only if the potential benefit clearly outweighs the potential risk, such as when there are few remaining treatment options. The three reported cases occurred in women who were either pregnant or postpartum, who were taking stavudine, didanosine, and other antiretroviral agents in combination. Two women had pancreatitis; the third did not. Two of the fatalities occurred during clinical trials; the third was reported via postmarketing surveillance performed worldwide. Postmarketing surveillance has also revealed several nonfatal cases of pancreatitis, with and without lactic acidosis or hepatic failure in pregnant women taking both stavudine and didanosine.

The Boxed Warning, Warnings, and Precautions sections of the drug labels already stated a risk of lactic acidosis, but BMS has broadened those sections to reflect the cases recently reported. A copy of the BMS letter to health professionals can be found at www.fda.gov / medwatch / safety / 2001 / safety01.htm#zerit. ■

Keep colleagues informed about drug shortages

The Center for Drug Evaluation and Research (CDER) lists drugs that are currently in short supply on the Food and Drug Administration Web site. The information may help pharmacists pacify doctors and patients who can't understand why they can't get the drug they need, in the formulation they need. The following is the drug shortage listing as of the end of January.

• Fentanyl (Taylor / Akorn, Abbott, ESI Lederle):

— due to unexpected increase in demand for product;

— all three manufacturers report back orders; projected availability will be posted as soon as possible.

• Isuprel and Isoproterenol Injection (Abbott):

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— due to manufacturing difficulties;

— contact Abbott customer support line at (800) Abbott3 for an emergency supply of the product.

• Mesantoin (mephenytoin) (Novartis Pharmaceuticals):

— due to discontinued manufacturing;

— drug is currently distributed by Novartis under a transition program; a small quantity may be obtained for use in transitioning patients to other anticonvulsants.

• Quinidine Gluconate (Eli Lilly, available through CDC Malaria Hotline):

— see link for additional information.

• Romazicon (flumazenil) (Roche Pharmaceuticals):

— due to manufacturing difficulties:

— Roche reports that Romazicon is available in 5 mL vials without back order; release date for 10 mL vials is unknown.

Products with limited distribution and those whose shortage has been resolved appear in separate lists on the following Web site: www.fda.gov/cder/drug/shortages/default.htm.

To report a drug shortage, health professionals and patients may contact CDER Drug Information at (888) INFOFDA or (888) 463-6332. ■

Feed Your Pocket Brain

Cut out the attached list and paste it into your pocket brain to have at hand the risk factors for stroke. Feel free to add your contribution to the pocket brain column of *Drug Utilization Review* by sending it to the editor at ruthnoland@hotmail.com.

Risk Factors for Stroke

- Increasing age — risk doubles for each decade after age 55
- Sex — incidence and prevalence of stroke are about equal for men and women; however, more than 50% of deaths resulting from stroke occur in women
- Heredity and race — family history increases risk; African Americans have a much higher risk of morbidity and mortality from stroke than whites, corresponding with a greater incidence of hypertension and diabetes; Asian-Pacific Islanders and Hispanics also have a high risk of stroke
- Prior stroke — risk is several times greater of a repeat stroke once you've had one
- Hypertension — BP of 140/90 or higher for an extended time is the most important risk factor for stroke
- Cigarette smoking — nicotine and carbon monoxide in cigarette smoke damage the cardiovascular system; use of oral contraception in addition to smoking greatly increases the risk of stroke
- Diabetes — an independent risk factor for stroke, even when diabetes is treated; strongly correlated with hypertension; elevated cholesterol and obesity exacerbate the risk
- Carotid artery disease — carotid arteries altered by atherosclerosis may become blocked with blood clots and cause strokes; peripheral artery disease associated with atherosclerosis is a risk factor for carotid artery disease
- Heart disease — puts individuals at more than twice the risk; atrial fibrillation, in particular, increases risk; heart attack is the major cause of death among stroke survivors
- TIA — transient ischemic attacks (TIAs) produce symptoms of stroke without lasting damage; TIAs are strong predictors of stroke; the occurrence of 1+ TIA raises the risk almost 10 times that of someone of the same sex and age without a history of TIA; emergency medical help should be sought immediately once a TIA is suspected
- Increased hemoglobin — moderate to marked increase in Hg thickens the blood and increases likelihood of clot formation
- Sickle cell anemia — "sickled" red blood cells carry less oxygen to the body and tend to stick to blood vessel walls, with the potential to block arteries to the brain, resulting in a stroke.

Adapted from American Heart Association at http://www.americanheart.org/Heart_and_Stroke_A_Z_Guide/strokeri.html

DRUG CRITERIA & OUTCOMES™

Dextroamphetamine/amphetamine (Adderall) for ADHD

By **Christy L. Collard**, PharmD
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Charleston

Indications:

Dextroamphetamine/amphetamine (Adderall) by Shire Richwood Inc., of Florence, KY, is indicated for use as a part of a total treatment program, including psychological, educational, social components, for a stabilizing effect in children diagnosed with attention deficit/hyperactivity disorder (ADHD); and for a syndrome of persistent patterns of inattention, hyperactivity, impulsivity, and emotional liability.[1,2] It is also indicated for narcolepsy, although there are no published trials to evaluate the drug for this indication.

Pharmacology:

Adderall is an amphetamine product that combines four amphetamine salts: the neutral sulfate salts of dextroamphetamine and amphetamine, dextroamphetamine saccharide, and amphetamine aspartate. Amphetamines are noncatecholamine, sympathomimetic agents, which have a stimulant effect on the central nervous system. Peripheral effects including elevation of systolic and diastolic blood pressure, respiratory stimulation, and weak bronchodilatory effects are also seen with amphetamines. The mechanism of action for the emotional and behavioral modification seen in children is unknown. Additionally, it is unknown how these emotional and behavioral abnormalities relate to the condition of the central nervous system.[1,2]

Pharmacokinetics:

Dextroamphetamine has an onset of action of two to three hours, achieves peak plasma concentrations in one to three hours, and has a duration of effect of four to 24 hours. Dextroamphetamine has extensive oral bioavailability. Cerebral spinal fluid concentrations of dextroamphetamine reach approximately 80% of plasma concentrations. The volume of distribution for dextroamphetamine is approximately 6 L/kg. It is extensively metabolized by the liver and is 17% to 37% renally eliminated. Dextroamphetamine is dialyzable by hemodialysis and peritoneal dialysis.[2]
Amphetamine has an onset of action of one to three hours, achieves peak plasma concentrations in two to four hours, and has a duration of effect of up to 10 hours. Amphetamine has good oral bioavailability. Cerebral spinal fluid concentrations of amphetamine reach approximately 80% of plasma concentrations. The volume of distribution for amphetamine is about 3.5 to 6 L/kg. It is primarily liver metabolized, and up to 37% is excreted by the kidney.[2]

Selected clinical trials:

Swanson and colleague[3] conducted a randomized, double-blind, cross-over study involving 30 children with ADHD. The study was designed to evaluate four different doses of Adderall (5 mg, 10 mg, 15 mg, 20 mg) administered orally. Patients were eligible for participation if they met the following inclusion criteria: age 7 to 14 years, *DSM-IV* diagnosis of ADHD, and a history of a clinically significant response to usual doses of methylphenidate (5 mg to 20 mg, administered orally in two to three divided doses). Patients were not eligible to participate in this study if they had any of the following: blood pressure readings outside the 95th percentile (according to age and gender), a WISC-III IQ rating of less than 80, abnormal physical exam, current use of nonstimulant medication for the treatment of ADHD, a comorbid disorder, or a history of aggressive behavior serious enough to prohibit participation in ordinary classroom activities. Participants

were evaluated over a seven-week period, which allowed six weeks for medications and an extra week to reschedule any missed weeks. For each week, seven identical capsules were provided, to be administered one capsule each morning. Capsules contained placebo, Adderall in doses of 5 mg, 10 mg, 15 mg, and 20 mg, or methylphenidate (dose determined by the subject's clinical history). All doses were administered orally. Patients were scheduled to participate in classroom, playground, and laboratory activities and were evaluated during these activities by the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale, the National Institute of Mental Health Collaborative Multisite Treatment Study of Children with ADHD impairment scale (MTA), and the permanent product (PERMP) measure of performance rating. Side effects of Adderall were also assessed using the MTA 10-item Stimulant Side Effect (SSE) scale. The SSE uses a four-point rating scale: not at all, just a little, pretty much, or very much.[3]

The study participants did not experience any serious or unusual side effects during the trial, and the measures of common psychostimulant side effects (e.g., insomnia, anorexia) were reported no more frequently than with placebo for most treatment weeks. Adderall-treated subjects showed improved behavior. There was a dose-dependent improvement in SKAMP and PERMP scores for the Adderall treatments. The duration of effect appeared to be dose-dependent, as well. Time to peak effect was shorter on average for methylphenidate (1.88 hours) at an average oral dose of 12.5 mg than for the Adderall 5 mg, 10 mg, 15 mg, and 20 mg doses (1.5, 2.6, 2.6, and 3.0 hours, respectively). The duration of effect was shorter, on average, for methylphenidate (3.98 hours) at an average oral dose of 12.5 mg, compared to the Adderall 5 mg, 10 mg, 15 mg, and 20 mg doses (3.52, 4.83, 5.44, and 6.4 hours, respectively). These data support that the use of Adderall is a treatment option for children affected with ADHD.[3]

Pliska and colleagues[4] conducted a three-week, randomized, double-blind, placebo-controlled, parallel-group study of Adderall involving 58 children diagnosed with ADHD. Children were evaluated three times daily using the Inattention/ Overactivity With Aggression (IOWA) scale by both teachers (morning and afternoon) and parents (evening). Side effects of treatment were assessed using the Multi-Modality Treatment of ADHD side effects scale. Doses of methylphenidate and Adderall were started at 5 mg, administered orally, for children weighing less than 60 pounds and 10 mg, administered orally, for children weighing more than 60 pounds. Week One dosing occurred once daily in the morning. For patients showing improvement for morning, afternoon, and evening with Adderall, the dosing was continued at the daily dose in the morning for Week Two. For patients who did not show improvement on either the morning or afternoon evaluation, the daily Adderall dose was doubled for Week Two. For patients who showed improvement in the morning and afternoon evaluations, but not in the evening evaluation, a second dose was added after school for Week Two. For the third week, if afternoon scores remained impaired, a noon dose was added, and for those patients who showed impaired evening scores, an after-school dose was added. For methylphenidate, the dosing algorithm was similar except that a noon dose could be added for Week Two. The patients receiving placebo adhered to either the Adderall or methylphenidate algorithm.[4]

The average daily doses of methylphenidate and Adderall were 25.2 +/- 13.6 mg and 12.5 +/- 4.1 mg, respectively. Several adverse effects (stomach ache and sadness/tearfulness) were more common in the Adderall treatment group compared to the placebo group. Adderall did not have a statistically different side effect profile when compared to methylphenidate. Adderall showed improvement in the IOWA morning and evening evaluations compared to methylphenidate ($p < 0.5$). It should
be noted that the results of this study are limited due to the possibility of underdosing of the methylphenidate group. The average daily dose of methylphenidate in this study was 0.43 mg/kg. The known required dose of methylphenidate is 0.3 to 0.8 mg/kg.[4]

Narcolepsy: The Food and Drug Administration approved Adderall for the indication of narcolepsy without any pivotal trials. In addition, Shire Richwood Inc., was unable to provide any information on the use of Adderall in narcolepsy.[5]

Adverse reactions:

The most common adverse effects experienced by patients taking Adderall are cardiovascular in nature and include palpitations, tachycardia, and blood pressure elevation. More serious adverse effects of cardiomyopathy have been reported in isolated cases associated with the long-term use

of amphetamines.[1,2] Reported central nervous system effects include stimulant effects such as overstimulation, restlessness, dizziness, insomnia, and euphoria. Dyskinesia, dysphoria, tremor, and headache have also been reported. Some patients may experience an exacerbation of motor tics, phonetic tics, and Tourette's syndrome or psychotic episodes while taking this product.[1,2] Gastrointestinal effects include dry mouth, unpleasant taste, diarrhea, and constipation. Anorexia and weight loss can also be seen with stimulant medication use.[1,2] Allergic effects include urticaria, and reported endocrine effects include changes in libido and impotence.[1,2]

Pregnancy/lactation:

Adderall is rated as a Pregnancy Category C.[1,2] There are no adequate, well-controlled human studies of Adderall in pregnant women to date. It is noted that there have been case reports of malformations in infants born to a mothers who took amphetamine products during pregnancy. There has been one case report of structural abnormalities in an infant born to a mother who took Adderall and lovastatin during the first trimester of pregnancy. Severe congenital bony deformity, tracheoesophageal fistula, and anal atresia were seen in this infant. For dextroamphetamine and amphetamine alone, several cases have been reported in which various malformations have occurred. Such malformations include cardiac deformities, exencephalia, and limb reduction defects.[2,6] Only in cases where the benefits justify the potential fetal risk, should amphetamines be administered in pregnant women. In addition, mothers taking amphetamines should be advised to abstain from breastfeeding, as amphetamines are excreted in human breast milk.[1,2,6,7]

Contraindications:

Adderall is contraindicated in patients who have a known hypersensitivity to sympathomimetic amines. Patients who suffer from advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or glaucoma should not use this product. In addition, use of Adderall is contraindicated in patients who experience agitated states or with a history of drug abuse. Adderall is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors, as a hypertensive crisis may result.[1,2]

ADHD notes

ADHD is a diagnosis applied to children and adults who consistently display certain characteristic behaviors over a period of time. The most common behaviors fall into three categories: inattention, hyperactivity, and impulsivity.

Inattention: difficulty keeping one's mind on any one thing; may get bored with a task after only a few minutes; may give effortless, automatic attention to activities and things enjoyed, but deliberate focus and attention to organizing and completing tasks or learning something new is difficult.

Hyperactivity: appearance of always being in motion; inability to sit still (as through a lesson); tend to squirm in seats and roam around rooms; intense feeling of restlessness in adults; attempt to accomplish several things at once, bouncing from one activity to the next.

Impulsivity: inability to curb immediate responses; characterized by reacting before thinking; will blurt out inappropriate comments; difficulty waiting for things they want. ■

Adapted from Attention Deficit Hyperactivity Disorder. National Institute of Mental Health, NIH Publication 96-3572, 1996 reprint. May be viewed online at http://www.nimh.nih.gov/publicat/adhd.cfm#adhd3.

Warnings:

Clinical experience suggests that, in psychotic children, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder. There are insufficient data to determine whether chronic administration of amphetamines may be associated with growth inhibition. Therefore, growth should be monitored during treatment with the drug. Adderall may impair the patient's ability to operate machinery or vehicles, and patients should be advised of this risk.[1,2]

Dosage and administration:

Dosage of amphetamines should be individualized, and the lowest effective dosage should be administered. Doses should be administered in the morning, if possible. Late-night doses should be avoided because insomnia may result. No dosage adjustments are recommended for patients experiencing renal or hepatic insufficiency. Adderall does not have any geriatric

dosage recommendations or recommendations for children younger than 3 years of age.[1,2]

For children 3 to 5 years of age, the recommended starting dose of Adderall is 2.5 mg daily, administered orally. Daily dosage may be adjusted at weekly intervals in increments of 2.5 mg (until the desired response is obtained). For children 6 years of age and older, the recommended starting dose is 5 mg daily. Alternatively, the dose may be divided twice daily. Daily dosage may be adjusted at weekly intervals in increments of 5 mg until the desired response is obtained. Only in rare instances is it necessary to prescribe a total daily dose of 40 mg or greater. The first dose of Adderall should be administered upon waking, and additional doses may be administered at intervals of four to six hours. If possible, treatment with Adderall should be interrupted occasionally, to assess whether behavioral symptoms persist and to evaluate whether continued therapy is necessary.[1]

Drug-drug interactions:

Gastrointestinal acidifying agents (e.g., fruit juice, vitamin C) may lower absorption of Adderall. Conversely, gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) may increase amphetamine absorption.[1,2] Amphetamines delay gastrointestinal absorption of ethosuxamide.[1,2] Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine) may increase urinary excretion of amphetamines by increasing the ionized species concentration of amphetamines. Conversely, urinary alkalinizing agents (e.g., acetazolamide, thiazides) may increase the nonionized species concentration of amphetamines, resulting in decreased urinary excretion of amphetamines.[1,2]

Amphetamines delay the intestinal absorption of phenobarbital and phenytoin, and co-administration may result in a synergistic anticonvulsant action. In cases of propoxyphene overdose, fatal convulsions may occur due to the potentiation of CNS stimulation with amphetamines. Amphetamines inhibit adrenergic blockers and the hypotensive effects of veratrum alkaloids. The hypotensive effects of antihypertensive agents and the sedative effect of antihistamine agents may be antagonized by amphetamine use. Lithium may inhibit the anorectic and stimulatory effects of amphetamines. Haloperidol may inhibit the CNS stimulant effects of amphetamines by blocking dopamine receptors. Similarly, chlorpromazine may inhibit the CNS stimulant effects of amphetamines by blocking dopamine and norepinephrine receptors. The analgesic effect of meperidine may be increased with amphetamine use. Amphetamines may potentiate the adrenergic effects seen with norepinephrine. Tricyclic antidepressant agents may have enhanced activity when used with amphetamines. Monoamine oxidase inhibitor agents slow the metabolism of amphetamines.[1,2]

Drug-laboratory test interactions:

Adderall use can result in elevated serum corticosteroid levels, with the greatest increase occurring in the evening. Additionally, Adderall can interfere with urinary determinations of steroids.[1]

Dosage forms available:

Adderall is available in four strengths (5 mg, 10 mg, 20 mg, 30 mg) in the form of an oral tablet.[1,8]

Potential for medication errors:

"Adderall" has the potential to be confused with "Inderal."[8] Inderal is a brand-name product containing propranolol, a beta adrenergic antagonist.

Discussion:

Clinical data support the efficacy of Adderall in the behavioral management of children with ADHD, and it appears to be comparable in efficacy, safety, and side effects to methylphenidate.[3,4] However, it should be noted that these trials may be flawed in their comparisons of Adderall to methylphenidate, and these results may be skewed in favor of Adderall.

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Verteporfin: For macular degeneration

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Indications:

Verteporfin (Visudyne), by Ciba Vision, of Duluth, GA, is approved for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.[1,2]

Pharmacology:

Following intravenous infusion, verteporfin is transported in the plasma primarily by lipoproteins. Upon activation by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Vessel occlusion results from the light-activated verteporfin causing local damage to neovascular endothelium. The damaged endothelium releases procoagulant vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation, and vasoconstriction. Verteporfin appears to selectively accumulate in neovasculature, including choroidal neovasculature. Animal models show some drug present in the retina, as well. Thus, it is possible that collateral damage to retinal structures such as the retinal pigmented epithelium and outer nuclear layer of the retina may occur following photoactivation. Following verteporfin therapy, the temporary occlusion of choroidal neovascularization has been confirmed by fluorescein angiography.[1,2]

Pharmacokinetics:

Following intravenous infusion, verteporfin exhibits a bi-exponential elimination half-life of approximately five to six hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg / m^2. Verteporfin is metabolized to a small extent to its di-acid metabolite by liver and plasma esterases. NADPH-dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin. Verteporfin is almost entirely eliminated in the feces, with less than 0.01% of the dose recovered in the urine. Half-life was increased by approximately 20% in a study of patients with mild hepatic insufficiency (defined as having two abnormal hepatic function tests at enrollment). However, area under the curve and Cmax were not significantly different from the control group.[1,2]

Selected clinical trials:

The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group conducted two multicenter, double-blind, placebo-controlled, randomized clinical trials involving 609 patients (verteporfin, n = 402; placebo, n = 207) with classic containing subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration.[3] The studies were conducted to assess if photodynamic therapy with verteporfin could safely reduce the risk of vision loss in patients with CNV secondary to age-related macular degeneration. Results from the two identical study protocols, which ran concurrently in North America and Europe, were published together.[3]

Patients were included in the studies if they met the following criteria: CNV secondary to age-related macular degeneration, CNV under the geometric center of the foveal avascular zone, evidence of classic CNV on fluorescein angiography, area of CNV at least 50% of the area of the total neovascular lesion, greatest linear dimension of lesion $\leq$ 5,400 nm, and age $\geq$ 50 years. Patients were excluded if the following criteria were present: tear of retinal pigment epithelium, any significant ocular disease, inability to obtain photographs to document CNV, history of treatment of CNV other than nonfoveal confluent laser photocoagulation, participation in another ophthalmic clinical trial or use of other investigational drugs within 12 weeks prior to the start of the study, active hepatitis or other clinically significant liver disease, porphyria, prior photodynamic therapy for CNV, intraocular surgery within last two months, or capsulotomy within last month in the study eye.[3]

Patients were randomized, in a 2:1 ratio, to

receive either verteporfin 6 mg/m^2 intravenously or placebo. Placebo consisted of intravenous administration of dextrose 5% in water, followed by the same light application used in the verteporfin group. A planned analysis of safety and efficacy was conducted at one year, with 94% of patients completing the one-year examination. During the course of the study, retreatment was allowed every three months if fluorescein angiograms showed any recurrence or persistence of leakage. At the one-year analysis, visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were statistically better in the verteporfin group ($p < 0.001$).[3]

The subgroup analysis of patients with predominantly classic CNV lesions (defined as an area of CNV occupying 50% or more of the area of the entire lesion) was more likely to exhibit a treatment benefit (verteporfin, n = 159; placebo, n = 84). For the primary efficacy endpoint (percentage of patients who lost less than three lines of visual acuity), this subgroup displayed a 28% difference between verteporfin and placebo (67% for verteporfin compared to 39% for placebo, $p < 0.001$). Severe vision loss (six or more lines of visual acuity from baseline) was seen in 12% of verteporfin-treated patients vs. 33% of placebo-treated patients.[3]

Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit. When assessed with less than three line-lost criteria, this group showed a 49% difference between treatment groups (77% vs. 27%). Severe vision loss was demonstrated in 10% of verteporfin-treated patients compared to 41% of patients treated with placebo. Those groups less likely to benefit from verteporfin therapy include: older patients (more than 75 years of age), patients with dark irises, patients with occult lesions, and patients with less than 50% classic CNV.[3]

The authors concluded that verteporfin photodynamic therapy is safe and effective for the treatment of patients with CNV secondary to age-related macular degeneration.[3]

Adverse reactions:

In clinical trials, the most commonly reported adverse reactions associated with verteporfin therapy were headache, injection-site reactions (e.g., extravasation, rash), and visual disturbances (e.g., blurred vision, decreased visual acuity, visual field defects). Less commonly reported adverse reactions were ocular treatment site reactions, cardiovascular effects (e.g., atrial fibrillation, hypertension, peripheral vascular disorder, and varicose veins), elevated liver function tests, and elevated serum creatinine. In up to 4% of patients, severe vision decreases, defined as four lines or more, have been reported within seven days of treatment. In some patients, partial recovery of vision was achieved. Following exposure to sunlight, photosensitivity reactions (skin sunburn) have occurred.[1-3]

Contraindications:

Verteporfin is contraindicated in patients with a known hypersensitivity to any active or inactive ingredients of this preparation and in patients with porphyria.[1,2]

Warnings/Precautions:

Following verteporfin therapy, patients should avoid exposure of skin and eyes to direct sunlight or bright indoor light for five days. Standard precautions should be taken with verteporfin infusion to avoid extravasation.[1,2]

In the event that extravasation occurs, the infusion should be stopped immediately and cold compresses should be applied. The extravasated area should be protected from direct light until the swelling and discoloration have faded to ensure that a local burn does not occur. If emergency surgery is necessary within 48 hours following extravasation, as much of the internal tissue as possible should be protected from intense light.[1,2]

If patients experience a severe decrease of vision of four lines or more within one week after treatment, they should not be retreated, at least until their vision completely returns to pretreatment level. At this point, the physician should consider the potential risk vs. potential benefit of treatment.[1,2]

There is no clinical experience with administration of verteporfin to patients with moderate to severe hepatic impairment; therefore, use in these patients should be carefully considered. There are no clinical data evaluating verteporfin therapy in anesthetized, humans; however, animal studies at a greater than tenfold higher dose showed that severe hemodynamic effects, including death, resulted from a verteporfin bolus injection.[1,2]

Incompatible lasers should not be used with verteporfin, as undertreatment, overtreatment, or damage to the surrounding tissue could occur.[1,2]

Pregnancy/lactation:

Verteporfin is rated pregnancy category C.

There are no adequate and well-controlled studies of verteporfin use in pregnant women. In animal studies, doses of 40- and 125-fold human exposure produced fetal abnormalities. Verteporfin should only be used in a pregnant patient if the potential benefit justifies the potential risk to the fetus. It is not known if verteporfin is excreted in breast milk. Caution should be used when verteporfin is administered to a woman who is nursing.[1,4,5]

Dosage and administration:

Verteporfin therapy is a two-step process requiring administration of verteporfin followed by activation of the drug with light from a nonthermal diode laser. Verteporfin is administered via intravenous infusion at a dose of 6 mg / m^2 given over 10 minutes. Lesion size determination, spot size determination, and light administration should be done as directed in the product labeling. The physician should re-evaluate the patient every three months, and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.[1,2]

The potential of a severe, possibly permanent decrease in vision exists with an overdose of verteporfin and / or light due to nonperfusion of normal retinal vessels. An overdose of verteporfin will also cause an increase in the duration of time that a patient remains photosensitive to bright light. For these patients, an extension in the photosensitivity precautions is recommended.[1,2]

Following verteporfin therapy, patients will become temporarily photosensitive (five days) and should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light (e.g., tanning salons, bright halogen lighting and high-power lighting) during this time period. If patients must go outdoors during daylight hours, they should protect themselves by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions. Patients should be encouraged to expose their skin to ambient indoor light as it will help inactivate the verteporfin in the skin through a process called photobleaching.[1,2]

Drug interactions:

To date, no drug interaction studies have been performed with verteporfin in humans. Verteporfin is rapidly eliminated by the liver, although metabolism is limited. Verteporfin does not appear to be metabolized via the cytochrome P450 system. However, calcium channel blockers, polymyxin B, or radiation therapy could enhance verteporfin uptake by vascular epithelium. Other photosensitizing agents could increase the potential for photosensitivity reactions. Drugs that scavenge radicals or quench active oxygen species could decrease verteporfin activity. Drugs that decrease clotting, vasoconstrictors, or platelet aggregation could decrease verteporfin efficacy.[1]

Drug-food interactions:

To date, there are no known drug-food interactions with verteporfin.[1]

Dosage form available:

Verteporfin is available in a 15 mg single-use vial, which is reconstituted with 7 mL of sterile water to a concentration of 2 mg / mL.[1,2]

Samples status:

Sampling of this agent would not be appropriate.

Filtration requirement:

Verteporfin must be administered using a syringe pump and in-line filter.[1,2]

Discussion:

Age-related macular degeneration (AMD) is the most common cause of legal blindness for people older than age 50, in the Western world. AMD has few treatment options and no proven preventative therapy. Laser photocoagulation is the one treatment proved to be effective in clinical trials, but only a minority of patients are eligible for this therapy. Verteporfin photodynamic therapy uses light-activated drugs to stop or slow abnormal cell growth in AMD. Phase I and II clinical trials have demonstrated the safety and short-term effects of verteporfin therapy on vision. Multicenter, randomized, placebo-controlled, double-blind, phase III trials with verteporfin are ongoing. The one-year follow-up data indicate that visual acuity, contrast sensitivity, and angiographic outcomes are significantly better in verteporfin-treated eyes than in placebo-treated eyes ($p < 0.005$). At the one-year analysis, 67% of verteporfin-treated eyes vs. 39% of placebo-treated eyes lost less than three lines of vision. Verteporfin is generally well-tolerated. Headache, injection-site reactions, and visual disturbances are the most commonly reported

adverse reactions. Verteporfin can safely reduce the risk of vision loss in eyes with predominantly classic choroidal neovascularization (area of classic CNV ³ 50% area of entire lesion). In the absence of occult CNV, the benefits are of an even greater magnitude. Verteporfin therapy is safe and effective for the treatment of predominantly classic subfoveal CNV secondary to AMD. Although verteporfin is expensive, it presents a unique therapeutic option for patients with CNV secondary to AMD.[1,6]

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New FDA Approvals

These drugs have received final approval from the Food and Drug Administration (FDA):

Mesalamine (Canasa) suppositories by Axcan Scandipharm Inc. Mesalamine has received approval for use in suppository form for the treatment of **active ulcerative proctitis**. The treating dose is 500 mg twice daily, but may be increased to 500 mg three times daily if there is an inadequate response after two weeks of therapy.

Antidepressant mirtazapine (Remeron SolTab) orally disintegrating tablet by Organon Inc. The FDA has granted approval for a new formulation of mirtazapine for relief of **depression** and its associated symptoms of **anxiety, insomnia, and reduced appetite**. Instead of having to be swallowed, this tablet dissolves on the tongue within 30 seconds.

Steroid prednisolone sodium phosphate (Orapred) oral solution by Ascent Pediatrics Inc. Orapred has received approval as a treatment for **children with asthma and other inflammatory conditions**. Each 5 mL of Orapred (prednisolone sodium phosphate 20.2 mg) is the equivalent of prednisolone 15 mg.

Tolterodine tartrate (Detrol) LA capsules by Pharmacia. The FDA has granted approval for the extended-release formulation of this agent for **overactive bladder** with symptoms of urinary urge incontinence, urgency, and frequency. Detrol LA is to be available in 2 mg and 4 mg capsules. ■

IN THE PIPELINE

Alliance Pharmaceutical Corp. has voluntarily **suspended enrollment** in its Phase III study with its perflubron emulsion (Oxygent) due to an imbalance in adverse events, namely stroke.

Aronex Pharmaceuticals received a **nonapproval letter** from the FDA for **tretinoin liposome for injection** (Atragen) as treatment for patients with acute promyelocytic leukemia who require tretinoin but who require it in an IV form. As part of the letter, the FDA noted that the proposed claim was not supported because the data did not establish the existence of the patient population described in the claim.

Cellegy Pharmaceuticals Inc. has been granted **patent protection** by the Canadian Intellectual Property Office for compositions used in the treatment of **anal disorders**. This patent covers Cellegy's nitroglycerin ointment (Anogesic) which is currently in Phase III clinical trials in the United States for treatment of anal fissures. Patents protecting this drug product now exist in the United States, Europe, Canada, and Singapore, and are pending in other countries. ■