

in patients with prostate cancer who receive androgen deprivation therapy, according to the company. Amgen is reviewing both letters “and will work with the FDA to determine the appropriate next steps regarding these applications,” the company indicated.

At a meeting in August, an FDA advisory committee voted that the benefits of denosumab for treating postmenopausal osteoporosis outweighed its risks, but did not support use of the

drug for other indications, including osteoporosis prevention, primarily because of concerns about its long-term safety. Denosumab, a human IgG2 monoclonal antibody, targets “an essential regulator” of osteoclasts, according to Amgen. It is also being studied for other conditions associated with bone loss, including rheumatoid arthritis, and for its potential to delay bone metastases. If approved, its trade name would be Prolia. ■

# Pretherapy Spinal Fractures Seen In Pediatric Rheumatic Disorders

BY AMY ROTHMAN SCHONFELD

PHILADELPHIA — Vertebral fractures are present in a significant percentage of children with rheumatic diseases, and these fractures appear prior to prolonged glucocorticoid exposure, according to Dr. Leanne M. Ward. “Vertebral fractures are an underrecognized complication of steroid-treated rheumatic disorders,” said Dr. Ward, director of the Pediatric Bone Health Clinical and

Research Programs at University of Ottawa. “The question is when the fractures first occur—in the course of the disease or steroid treatment.”

Investigators from the Canadian STOPP (Steroid-Associated Osteoporosis in the Pediatric Population) Consortium evaluated the spine health of 134 children (89 girls; median age, 10 years) with rheumatic conditions.

In all, 30 children had juvenile dermatomyositis (JDM), 28 had juvenile idiopathic arthritis excluding systemic JIA, and 76 were diagnosed with other rheumatic disorders (systemic lupus erythematosus, systemic vasculitides, systemic JIA, and others).

The children underwent thoracolumbar spine x-rays and lumbar spine areal

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>6% difference) are shown in Table 2.

**Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo**

ADVERSE EVENTS %	Placebo Epoprostenol (n = 131)	Revatio Epoprostenol (n = 134)	Placebo-Subtracted %
Headache	34	57	23
Edema <sup>^</sup>	13	25	14
Dyspepsia	2	16	14
Pain in extremity	6	17	11
Diarrhea	18	25	7
Nausea	18	25	7
Nasal congestion	2	9	7

<sup>^</sup>includes peripheral edema

## Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

### Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see Warnings and Precautions].

### Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Warnings and Precautions].

### Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

## DRUG INTERACTIONS

### Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

### Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended [see Warnings and Precautions].

### Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of

standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

### Amlodipine

When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category B

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m<sup>2</sup> basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m<sup>2</sup> basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

### Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

### Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

### Renal Impairment

No dose adjustment is required (including severe impairment CL<sub>cr</sub> < 30 mL/min).

## OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m<sup>2</sup> basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

## PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
- Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

## RX only

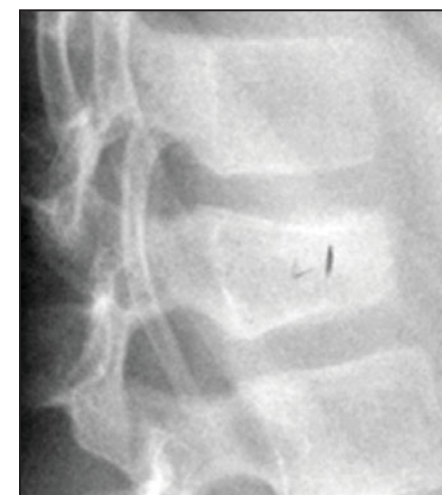
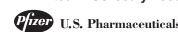
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This image shows a fracture at L1 in a girl with JDM who takes glucocorticoids.

bone mineral density (LS aBMD) evaluation within 30 days of beginning glucocorticoid therapy.

A total of 7% of the group (9 of 134) had vertebral fractures. In these nine children, six patients had a single vertebral fracture and three patients had 2-5 fractures, for a total of 13 fractures. Three of the fractures (23%) were moderate and the rest were mild. Most fractures were located in the midthoracic and upper lumbar regions, said Dr. Ward at the annual meeting of the American College of Rheumatology. Although the mean LS aBMD scores for the group were lower than the norm (-0.6 plus or minus 1.22; *P* less than .001), LS aBMD did not predict the development of vertebral fractures. The odds for fracture were increased 10-fold if the child reported back pain.

The STOPP Consortium was founded in 2003 as a Canadian national pediatric bone health working group of investigators from 12 tertiary children's hospitals.

Dr. Ward recommends that children with rheumatic diseases undergo baseline spine radiographs at diagnosis and then annually, or more frequently if they have new-onset back pain. Children with vertebral fractures who have back pain may be candidates for bisphosphonate therapy, said Dr. Ward.

Dr. Ward reported having a business relationship with Novartis. ■