



## POLICY & PRACTICE

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### College Overhauls CME

The American College of Cardiology announced that it is abandoning its current model for continuing medical education at scientific sessions, essentially to segregate industry-sponsored symposia from other sessions. The college "was prompted in part by ongoing concerns about real and/or perceived bias in interactions with industry, specifically related to non-independence of certified satellite symposia," said the group in a statement. There will be two educational tracks starting with next year's annual scientific session: One will have in-depth sessions developed by the ACC, and the other will be made up of uncertified satellite symposia. The latter can be industry sponsored and will be managed through the ACC's business development division. The policies guiding those seminars will be consistent with the Food and Drug Administration's and other regulatory agencies' rules governing industry-sponsored CME. "The move is important because it will allow for transparency in the two separate approaches and meet the educational needs of our members," said Dr. Rick Nishimura, cochair of the college's 2012 annual scientific session next March.

### Advocacy for Cardiology

The ACC's advocacy committee issued its five policy priorities for 2011. No. 1 is to overhaul the physician payment system by — among other efforts — repealing the Sustainable Growth Rate formula for Medicare payments. No. 2: Make sure cardiologists are part of new care-delivery plans stemming from health reform, such as Accountable Care Organizations.

Third is tort reform, and the advocacy committee's fourth priority is to help ACC members get ready to meet meaningful use criteria for health information technology. Finally, the committee said that it would also stay on top of coding changes, imaging-accreditation requirements, and the FDA's device-safety initiatives.

### FDA Device Review Questioned

The Government Accountability Office said that the FDA has not done enough to ensure the efficiency and effectiveness of its recall procedures for high-risk medical devices. Back in January 2009, the GAO found fault with the 510(k) device-approval process and recalls. The agency is again urging the FDA to quickly issue final rules to more strictly and clearly regulate 510(k) devices. Since the 2009 report, the FDA has published a strategic plan but issued a final rule on only one type of device, the GAO said. The agency is not collecting data that would let it identify risks

posed by devices, even though 3,510 were voluntarily recalled for problems in 2005-2009, said the GAO. "Taken together, GAO's preliminary work suggests that the combined effect of these gaps [in the FDA's recall process] may increase the risk that unsafe medical devices could remain on the market," said the new report.

### FDA Sued Over Generic Lipitor

Generic drugmaker Mylan has sued to force the FDA to speed up the introduction of generic versions of Pfizer's blockbuster drug Lipitor (atorvastatin). Mylan and its Indian partner, Matrix Laborato-

#### REVATIO® (SILDENAFIL)

##### Brief Summary of Prescribing Information

**INDICATIONS AND USAGE:** REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

##### DOSAGE AND ADMINISTRATION

##### Pulmonary Arterial Hypertension (PAH) REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

##### REVATIO Injection

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

##### CONTRAINDICATIONS

##### Use with Organic Nitrates

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

##### Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

##### WARNINGS AND PRECAUTIONS

##### Cardiovascular Effects

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosentan therapy.

##### Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see Drug Interactions]. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

##### Effects on Bleeding

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

##### Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A inhibitors with REVATIO is not recommended.

##### Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors [see Adverse Reactions].

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

##### Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [see Adverse Reactions].

##### Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

##### Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

##### Pulmonary Hypertension Secondary to Sickle Cell Anemia

In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established.

##### ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension [see Warnings and Precautions]
- Vision loss [see Warnings and Precautions]
- Hearing loss [see Warnings and Precautions]
- Priapism [see Warnings and Precautions]
- Vaso-occlusive crisis [see Warnings and Precautions]

##### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

**Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo**

ADVERSE EVENTS %	Placebo (n=70)	Revatio 20 mg TID (n=69)	Placebo-Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

nos: Not otherwise specified

## INDEX OF ADVERTISERS

#### Abbott Laboratories

Niaspan 15-16

#### Arbor Pharmaceuticals, Inc.

Nitrolingual 17-18

#### AstraZeneca L.P.

Atacand 3-5

#### Bayer HealthCare LLC

Aspirin 29

#### Boehringer Ingelheim Pharmaceuticals, Inc.

Pradaxa 9-12

#### Daiichi Sankyo, Inc.

Welchol 34a-34b, 35

#### Daiichi Sankyo, Inc. and Lilly USA, LLC

Effient 20-25

#### Forest Laboratories, Inc.

Bystolic 31-34

#### LipoScience Inc.

Corporate 6a-6b

#### Otsuka America Pharmaceutical, Inc.

SAMSCA 12a-12d

#### Pfizer Inc.

Revatio 38-40

#### University of Pittsburgh Medical Center

Corporate 27

#### Verathon Inc.

AortaScan 19

ries, said they could be ready to sell generic atorvastatin in late June. The companies claim the FDA must allow generic versions to enter the market then because Pfizer's key patent on Lipitor expires that month. Rival generic drug-maker Ranbaxy Laboratories has agreed in a patent settlement with Pfizer to wait until Nov. 30 to bring generic atorvastatin to market, when Ranbaxy expects to have exclusive rights to market the generic for 6 months. However, Ranbaxy may not be ready to market its product by November, pushing back Mylan's generic introduction even further, the company

said in its lawsuit. In addition, Mylan claims that Ranbaxy may have violated FDA rules in submitting its application, making it ineligible for the 6-month, exclusive-rights period for atorvastatin.

### Medicine Has Economic Power

Office-based physicians contributed \$1.4 trillion in economic activity in 2009 and supported 4 million jobs nationwide, according to a report from the American Medical Association. The report, prepared by the Lewin Group, calculates the state-by-state impact of the 638,000 office-based physicians in the United

States. In total, they provided \$833 billion in wages and benefits and generated \$63 billion in state and local tax revenues in 2009, the report said. On average, each office-based physician supported \$2.2 million in economic output and 6.2 jobs, including his or her own.

### Medical Boards Fail on Discipline

State medical boards failed to discipline more than half of doctors who either lost their clinical privileges or had them restricted by the hospitals where they worked, according to a report from advocacy group Public Citizen. In all,

10,672 physicians were listed in the National Practitioner Data Bank as having restricted or revoked clinical privileges, yet 5,887 (55%) of them did not see any licensing action from their states, the group reported. Of those escaping licensing actions, 1,119 had been otherwise disciplined for incompetence, negligence, or malpractice, and 605 were disciplined for substandard care, the report said. Hospital boards had identified 220 of the otherwise-unsanctioned doctors as "an immediate threat to health or safety," according to Public Citizen.

—Alicia Ault

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately colorizing to vision, but also increased sensitivity to light or blurred vision. The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

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=70)	Revatio 20 mg TID Epoprostenol (n=69)	Placebo-Subtracted
Headache	34	57	23
Edema <sup>a</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>a</sup>includes peripheral edema

### REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

### 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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