Sildenafil Citrate (Revatio) for the Treatment of Pulmonary Arterial Hypertension

Amber Bell, PharmD Candidate, Myesha Davis, PharmD Candidate, Fran Close, PhD, Marlon Honeywell, PharmD, and Evans Branch III, PharmD

INTRODUCTION
Pulmonary arterial hypertension (PAH) results from continuously high blood pressure (BP) in the pulmonary artery. In patients with PAH, the BP is usually greater than 25 mm Hg at rest and above 30 mm Hg with exercise.1

The cause of pulmonary hypertension may be idiopathic or familial in nature, but it may also be congenital or related to collagen vascular disease, human immunodeficiency virus (HIV), portal hypertension, and the use of recreational or therapeutic drugs (e.g., amphetamines, appetite suppressants, and cocaine).2

*Idiopathic* PAH is a form of primary pulmonary hypertension (PPH).3 A patient with PAH may experience fatigue, breathlessness, cyanosis of the lips, palpitations, chest pain, and syncope. Ultimately, lower-extremity edema is present around the ankles.

Right-sided congestion, consisting of increased jugular venous pressure, ascites, and hepatomegaly, may occur, leading to right ventricular heart failure. If PAH remains untreated, the risk of mortality is increased.1,4

The incidence of PPH ranges from one to two cases per million people in the general population.5

INDICATIONS
The World Health Organization (WHO) has classified PAH into several categories. Sildenafil citrate (Revatio, Pfizer) is an oral treatment that has been approved by the FDA to improve the exercise ability of patients in New York Heart Association Class I (Table 1). Revatio is a new formulation of Pfizer’s Viagra, which is indicated for erectile dysfunction. The efficacy of sildenafil has not been evaluated in patients currently receiving therapy with bosentan (Tracleer, Actelion), another agent approved for patients with PAH.6

PHARMACOLOGY
Sildenafil inhibits cyclic guanosine monophosphate (cGMP) and is selective for phosphodiesterase type 5 (PDE5), thereby inhibiting nitric oxide. This action results in the relaxation of pulmonary vascular smooth muscle and promotes vasodilation in smooth muscle. Sildenafil thus increases cGMP within pulmonary vascular smooth-muscle cells, resulting in relaxation. In patients with pulmonary hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, to vasodilation in the systemic circulation.6

PHARMACOKINETICS
Absorption and Metabolism
Sildenafil is absorbed rapidly after oral administration, with an absolute bioavailability of about 40%. In the fasting state, the peak plasma concentration (Cmax) is obtained within 30 to 120 minutes (median, 60 minutes) of oral dosing. With high-fat meals, the rate of absorption is reduced; the time to peak levels (Tmax) is delayed by 60 minutes, and the Cmax is reduced by about 29%. Sildenafil is distributed into the tissues, as indicated by the mean steady-state volume of distribution (Vss) of 105 liters.

Both sildenafil and N-desmethyl, a major active circulating metabolite, are 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.5

Sildenafil is metabolized by hepatic microsomal cytochrome P450 isoenzymes CYP 3A4 and CYP 2C9. CYP 3A4 is the major metabolizing enzyme and is derived from the N-desmethylation of sildenafil. N-desmethyl’s PDE selectivity is similar to that of sildenafil. Its potency for PDE5, in vitro is approximately 50% of that of the parent drug.

In normal, healthy patients, the metabolite’s plasma concentrations are about 40% of those observed for sildenafil and the metabolite accounts for about 20% of sildenafil’s pharmacological effects. In patients with PAH, the ratio of the metabolite to sildenafil is higher.

Sildenafil and the active metabolite have terminal half-lives of about four hours. Inhibitors of CYP450 3A4 such as ritonavir (Norvir, Abbott), ketoconazole (Nizoral, Janssen), and itraconazole (Sporanox, Janssen), as well as non-specific CYP inhibitors such as cinetidine (Tagamet, GlaxoSmithKline), may increase plasma levels of sildenafil. N-desmethyl is then further metabolized to inactive compounds.

Sildenafil is eliminated as metabolites; about 80% of the oral dose is eliminated in the feces, and about 13% is excreted in the urine.6

SPECIAL POPULATIONS
Geriatric Patients
Age may be a consideration in the administration of other medications, but the impact of age, sex, race, and renal or hepatic dysfunction has not had statistically significant effects on the pharmacokinetics of sildenafil.

Healthy geriatric patients aged 65 years or older had a reduced clearance of sildenafil; their free plasma concentrations were approximately 40% more than those seen in healthy volunteers of 18 to 45 years of age.
Patients with Renal Insufficiency

Subjects with mild renal insufficiency (a creatinine clearance [CrCl] from 50 to 80 ml/minute) and those with moderate renal insufficiency (a CrCl from 30 to 49 ml/minute) did not show renal impairment after taking a single oral dose of sildenafil 50 mg. In patients with severe renal impairment (a CrCl below 30 ml/minute), clearance of the drug was decreased. The result was a doubling of the area-under-the-curve (AUC) concentration and the C<sub>max</sub> in these patients, compared with volunteers of the same age who did not have renal impairment.

Patients with Hepatic Insufficiency

In patients with hepatic cirrhosis, the CrCl of sildenafil was reduced, resulting in elevated AUC concentrations (84%) and in the C<sub>max</sub> (47%), compared with volunteers of the same age with no hepatic impairment. Patients with severe hepatic impairment were not evaluated.6

**Efficacy**

**Bhatia et al.**7

In a retrospective analysis, Bhatia and colleagues reviewed the medical records of 13 patients with PAH who were receiving empirical adjunctive sildenafil therapy. The study was conducted at the Mayo Clinic’s intensive care unit (ICU) in Rochester, Minnesota between November 1, 2000, and August 31, 2001. The objective was to determine the immediate and long-term effects of adding sildenafil to therapeutic regimens containing bosentan (Tracleer), a calcium-channel blocker, or intravenous epoprostenol (Flolan, GlaxoSmithKline) in patients with PAH.

The research team obtained baseline measurements of patients’ systemic arterial pressure, pulmonary arterial pressure, right atrial pressure, pulmonary capillary wedge pressure, thermodilution cardiac output, and systemic arterial and mixed venous oxygen saturations. Each patient received a 25-mg oral dose of sildenafil. Every measurement was repeated at one to two, four, and eight hours. Oxygen saturation was measured only at the first interval.

After the last measurement interval, the investigators repeated the same procedure for all patients using 50-, 75-, and 100-mg doses of sildenafil for 24 to 48 hours as long as the systemic systolic BP was below 90 mm Hg during hemodynamic monitoring. The long-term effects of this study were evaluated according to noninvasive right ventricular systolic pressures, the right ventricular index of myocardial performance, and a six-minute walking test (Table 2). Of the 13 participants, 10 were discharged from the hospital and resumed taking the highest tolerated dose of sildenafil every eight hours. All participants returned for follow-up. The researcher concluded that patients receiving empirical adjunctive sildenafil demonstrated an immediate pulmonary vasodilator effect (Table 3). However, the long-term effect on right-sided heart function and functional status was unclear. Further studies are needed.7

**Ghofrani et al.**8

A randomized, controlled, open-label trial, performed in an intensive care unit (ICU), included 30 patients (23 women and seven men) with severe PAH (n = 16), chronic thromboembolic pulmonary hypertension (n = 13), or pulmonary hypertension caused by aplasia of the left pulmonary artery (n = 1). All of the patients had either Class III or IV PAH, according to the New York Heart Association guidelines. The goal was to evaluate the safety and efficacy of oral sildenafil alone and in combination with inhaled iloprost (Ventavis, CoTherix, Inc.), a prostacyclin analogue, for the treatment of PAH.

Patients were excluded from the trial if they had PAH secondary to chronic obstructive pulmonary disease, pulmonary venous congestion, congenital heart disease, or acute or chronic inflammatory lung disease. Patients were not eligible to enroll if they were pregnant, were documented to be using insufficient contraceptive measures, or had received previous PDE inhibitors, including theo-

### Table 1  New York Heart Association/World Health Organization Functional Assessment of Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Symptoms do not limit physical activity. Ordinary physical activity does not cause undue discomfort.</td>
</tr>
<tr>
<td>II</td>
<td>There is slight limitation of physical activity. The patient is comfortable at rest yet experiences symptoms with ordinary physical activity.</td>
</tr>
<tr>
<td>III</td>
<td>There is marked limitation of physical activity. The patient is comfortable at rest yet experiences symptoms with minimal activity.</td>
</tr>
<tr>
<td>IV</td>
<td>There is an inability to carry out any physical activity. The patient may experience symptoms even at rest. Discomfort is increased by any physical activity. The patient manifests signs of right-sided heart failure.</td>
</tr>
</tbody>
</table>


### Table 2  Long-Term Effects of Orally Administered Sildenafil*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular systolic pressure</td>
<td>89 ± 24</td>
<td>83 ± 27</td>
<td>.1</td>
</tr>
<tr>
<td>Right ventricular index of myocardial performance</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>.8</td>
</tr>
<tr>
<td>Six-minute walk (meters)</td>
<td>444.7 ± 111.5</td>
<td>451.3 ± 114.7</td>
<td>.8</td>
</tr>
</tbody>
</table>

* Right-sided heart function and functional status evaluations were performed for nine patients. All values are mean ± standard error of the mean.

Each patient initially received inhaled short-term nitric oxide; a maximum vaso-dilatory response of 20 to 40 parts per million was required. After hemodynamic parameters returned to baseline values, aerosolized iloprost 2.8 mcg was given via ultrasonic nebulization. Hemodynamic variables and gas exchange variables were then assessed in all treatment groups following therapy (Table 4).

After the hemodynamic variables returned to baseline, patients were randomly assigned to receive 12.5 mg of oral sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost, or 50 mg of sildenafil plus inhaled iloprost. Baseline hemodynamic profiles and gas exchange variables were then assessed in all treatment groups following therapy.

Table 3: Immediate Hemodynamic Effects of Orally Administered Sildenafil*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>Peak (P value)</th>
<th>Trough (P value)</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (L/minute)</td>
<td>6.2 ± 1.8</td>
<td>7.2 ± 2.8 (.4)</td>
<td>6.7 ± 3.4 (.41)</td>
<td>8.2 ± 2.8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>90 ± 11</td>
<td>80 ± 15 (.1)</td>
<td>80 ± 12 (.01)</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>48 ± 11</td>
<td>43 ± 9 (.01)</td>
<td>44 ± 12 (.01)</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>MPAP/MAP</td>
<td>0.5 ± 0.1</td>
<td>.6 ± .2</td>
<td>.6 ± .1</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>80 ± 19</td>
<td>71 ± 18 (&lt;.001)</td>
<td>73 ± 20 (.01)</td>
<td>65 ± 17</td>
</tr>
<tr>
<td>PVR index (U)</td>
<td>8.6 ± 3.5</td>
<td>6.7 ± 2.4 (.001)</td>
<td>8.3 ± 5.0 (.73)</td>
<td>5.7 ± 2.1</td>
</tr>
<tr>
<td>Right arterial pressure (mm Hg) (n = 12)</td>
<td>7.0 ± 4.0</td>
<td>5.8 ± 2.0 (.42)</td>
<td>5.3 ± 2.7 (.16)</td>
<td>2.3 ± 1.2</td>
</tr>
</tbody>
</table>

*All values are mean ± standard error of the mean. MAP = mean arterial pressure; mm Hg = millimeters of mercury; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance. Data from Bhatia S, Frantz R, Severson C, et al. Mayo Clin Proc 2003;78:1207–1213.7

Table 4: Hemodynamic Baseline Profile with Sildenafil Alone and in Combination with Inhaled Iloprost

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Heart Rate (beats/minute)</th>
<th>Mean Systemic Arterial Pressure (mm Hg)</th>
<th>Mean Pulmonary Arterial Pressure (mm Hg)</th>
<th>Pulmonary Vascular Resistance (L/minute per m²)</th>
<th>Cardiac Index (dyne/sec per cm)</th>
<th>Arterial Oxygen Saturation (%)</th>
<th>Mixed Venous Oxygen Saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 12.5 mg*</td>
<td>73 ± 10.1</td>
<td>89 ± 14.6</td>
<td>53 ± 11.9</td>
<td>1.86 ± 0.8</td>
<td>1,325 ± 728</td>
<td>95 ± 5.0</td>
<td>60 ± 12.4</td>
</tr>
<tr>
<td>Sildenafil 50 mg†</td>
<td>73 ± 16.7</td>
<td>100 ± 11.9</td>
<td>57 ± 16.4</td>
<td>1.95 ± 0.3</td>
<td>1,262 ± 735</td>
<td>96 ± 2.0</td>
<td>59 ± 10.7</td>
</tr>
<tr>
<td>Sildenafil 12.5 mg plus iloprost‡</td>
<td>67 ± 6.9</td>
<td>93 ± 7.4</td>
<td>53 ± 11.6</td>
<td>1.86 ± 0.5</td>
<td>1,230 ± 521</td>
<td>94 ± 3.7</td>
<td>60 ± 10.6</td>
</tr>
<tr>
<td>Sildenafil 50 mg plus iloprost§</td>
<td>82 ± 12.4</td>
<td>98 ± 14.1</td>
<td>59 ± 11.6</td>
<td>1.63 ± 0.3</td>
<td>1,471 ± 577</td>
<td>94 ± 3.4</td>
<td>51 ± 11.6</td>
</tr>
</tbody>
</table>

The number (n) of patients randomized into each treatment group (n = 7*: n = 8†: n = 7‡: n = 8§). Data from Ghofrani H, Wiedemann R, Rose F, et al. Ann Intern Med 2002; 136:515–522. Copyright 2002, American College of Physicians.8
nation therapies. Patients taking sildenafil 50 mg alone and iloprost alone had similar hemodynamic profiles, but these regimens demonstrated less potency than the combination therapies.8

ADVERSE EFFECTS

In a placebo-controlled trial, sildenafil was associated with more adverse drug events (ADEs) in 3% or more of patients taking the recommended daily dose (20 mg three times daily) than in subjects taking placebo. These ADEs were characterized as mild to moderate.

At the placebo dose, the incidence of retinal hemorrhage was 1%; at the recommended sildenafil dose, 1.4%; and at all sildenafil doses, 1.9%. However, these patients tended to have other risk factors for hemorrhage, including the simultaneous use of anticoagulant therapy. Commonly reported ADEs in patients taking sildenafil citrate are listed in Table 5.6

CONTRAINDICATIONS

Sildenafil potentiates the hypotensive effects of nitrates, and its use is thus contraindicated for patients who are using organic nitrates in any form, either regularly or intermittently. Patients with a known hypersensitivity to any component of the tablet should not use the product.6

DRUG INTERACTIONS

Sildenafil is extensively metabolized by CYP450 3A4 and, to a lesser degree, by CYP 2C9. Substrates of CYP 3A4 that are coadministered with this drug, or in combination with CYP 3A4 substrates and beta blockers, can either increase or decrease serum levels of sildenafil. Drugs that inhibit the CYP 3A4 isozyme include ketoconazole, itraconazole, ritonavir, cimetidine, erythromycin, and saquinavir (Fortovase, Roche), whereas bosentan decreases serum concentrations of sildenafil.

Concurrent administration of sildenafil and the alpha blocker doxazosin mesylate (Cardura, Pfizer) infrequently resulted in symptomatic postural hypotension, including dizziness and light-headedness. The use of vitamin K with sildenafil resulted in a higher incidence of bleeding, predominantly associated with epistaxis.6

DOSAGE AND ADMINISTRATION

Revatio is administered as a 20-mg tablet, to be taken orally three times a day, four to six hours apart, with or without regard to food.6 It is available as a white, film-coated, round tablet to distinguish it from Viagra, which is blue and oval-shaped.10 Viagra is available as 25-, 50-, and 100-mg tablets.

CONCLUSION

Treatment options for the management of PAH are continuously evolving. The use of vasodilator agents to decrease PVR by reducing inflammatory mediators, remodeling of pulmonary vessel walls, vasoconstriction, and thrombosis has vastly improved the poor prognosis associated with PAH. Because the rapid progression of this disease is associated with right-sided heart failure and ultimately death, adjunctive or augmentation therapies can aid in decreasing the high risk of premature morbidity and mortality, improving survival rates, and enhancing patient compliance.9

Sildenafil citrate is the first oral selective cGMP-specific PDE5 inhibitor indicated for the treatment of PAH and is designed to improve exercise capacity.6 It shows remarkable short-term hemodynamic effects in patients already receiving therapy for PAH.7–9 However, more studies of its long-term use are warranted.

REFERENCES