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 60 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (Epoprostenol = 131)</th>
<th>Epoprostenol (n = 131)</th>
<th>Placebo-Subtracted (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>51</td>
<td>17</td>
</tr>
<tr>
<td>Edema</td>
<td>13</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>17</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Includes peripheral edema

**REVATIO Indications**

REVATIO-Epoprostenol Injection was studied in a 69-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 RV 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 cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischaemic attack, hypertension, pulmonary edema, 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-arteriolar 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 preexisting 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, hypercholesterolemia, 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, 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 of REVATIO. The following list of 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.

**Drug Interactions**

**Alpha-blockers**

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

**Alpha-adrenergic receptor antagonists**

Caution when co-administering alpha-adrenergic receptor antagonists with REVATIO because of additive blood pressure-lowering effects [See Warnings and Precautions].

**Overdosage**

In drug-drug interaction studies, 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 1.6 mmHg systolic and 0.7 mmHg diastolic.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Sildenafil has been detected in human plasma following oral administration of radiolabelled compound to human volunteers. It is not known if sildenafil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman. [See Warnings and Precautions].

**Pediatric Use**

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

**Geriatric Use**

In drug-drug interaction studies, 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 1.6 mmHg systolic and 0.7 mmHg diastolic.

**Disclosures:** The study is funded by the Dutch League Against Rheumatism and Medac, a German manufacturer of methotrexate. Dr. Wulffraat reported having no conflicts of interest.