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*APPLICATION NUMBER:*

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**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 203,109  
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Product: Revatio® (sildenafil)  
Indication: Pediatric pulmonary arterial hypertension  
Applicant: Pfizer  
Review Division: Cardiovascular and Renal Products  
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# 1 Executive Summary

## 1.1 Introduction

Sildenafil selectively inhibits cyclic GMP (cGMP) phosphodiesterase 5 (PDE5). Prominent effects of PDE5 inhibition include dilation of vascular and visceral smooth muscle and inhibition of platelet aggregation. Sildenafil is currently approved for treatment of erectile dysfunction and for treatment of pulmonary arterial hypertension in adults.

## 1.2 Brief Discussion of Nonclinical Findings

No new nonclinical pharmacology, pharmacokinetic or toxicology studies were submitted with this NDA. The nonclinical studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction) and for NDA 21845 (for treatment of pulmonary hypertension in adults).

In NDA 21845, the sponsor reported one in-vivo study that evaluated the pulmonary and systemic hemodynamic effects of intravenous sildenafil in an anesthetized, hypoxic dog model. Among other findings, that study demonstrated that sildenafil infusion produced much greater decreases in pulmonary vascular resistance and in pulmonary artery pressure than in systemic vascular resistance or systemic arterial pressure. The sponsor has not reported in-vitro or in-vivo studies that were specifically designed to evaluate pulmonary vascular effects of sildenafil in neonatal or pediatric animals.

The FDA Medical Officer who reviewed this NDA indicated that the pediatric clinical studies submitted with this NDA demonstrate a late, dose-related increase in mortality among patients who participated in a long-term extension study following participation in a sixteen-week, randomized, placebo-controlled trial. The majority of deaths appear to be the result of worsening pulmonary hypertension, cardiac failure, cardiogenic shock, and ventricular fibrillation, which are expected modes of death in this patient population.

The adverse effect on mortality was unexpected. Increased mortality had not previously been reported for adult or pediatric pulmonary artery hypertension (PAH) patients treated with sildenafil, including the adult PAH patients studied for NDA 21845. The animal studies of sildenafil submitted by the sponsor with NDAs 20895 and 21845 found large safety margins in the healthy animals (mice, rats and dogs) used in the safety pharmacology and toxicology studies completed for this drug. None of the animal studies submitted by the sponsor suggested that treatment with sildenafil might adversely affect pulmonary or cardiac function in patients with PAH.

Two hypotheses by which sildenafil treatment might contribute to increased cardiac and/or pulmonary mortality are discussed below: 1) adverse cardiac effects (potentially including cardiac arrhythmias and progression of heart failure) secondary to a cardiac inotropic effect, possibly mediated by increased levels of cAMP, and 2) dilation of

regional pulmonary vasculature that should be constricted by hypoxia, potentially promoting intra-pulmonary shunting and/or ventilation-perfusion mismatch.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

There are no nonclinical findings that would prevent approval of this NDA. The NDA is approvable from a nonclinical standpoint. However, the lack of significant nonclinical safety signals does not ameliorate the adverse clinical outcomes observed in the clinical studies reported with this NDA.

#### **1.3.2 Additional Non Clinical Recommendations**

There are no additional nonclinical recommendations. However, if future clinical study requests are made to the sponsor that relate to pulmonary artery hypertension indications (adult or pediatric), it could be suggested that future clinical studies include: 1) evaluation of the possibility that sildenafil treatment might produce right ventricular inotropic effects, particularly at timepoints when right ventricular hypertrophy or failure is present (and when PDE5 levels in the right ventricle might be upregulated), and 2) evaluation of the possibility that sildenafil treatment might promote adverse intra-pulmonary shunting and/or ventilation-perfusion mismatch, including during bouts of pneumonia.

#### **1.3.3 Labeling**

I have no recommendations for changes to labeling.

## **2 Drug Information**

### **2.1 Drug**

CAS Registry Number: 171,599-83-0

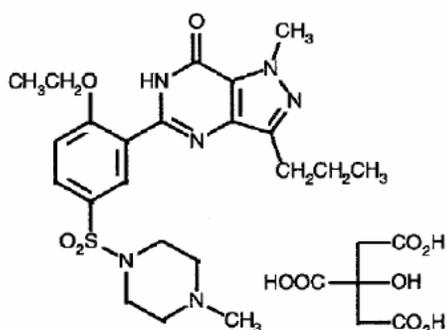
Generic Name: sildenafil citrate

Code Name: UK-92,480; UK-92,480-10

Chemical Name: 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine citrate salt

Molecular Formula/Molecular Weight:  $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

## Structure or Biochemical Description



Pharmacologic Class: Phosphodiesterase 5 (PDE5) inhibitor; cyclic guanosine monophosphate (cGMP)-specific

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20895 – sildenafil for treatment of erectile dysfunction  
 NDA 21845 – sildenafil for treatment of pulmonary arterial hypertension  
 IND 46863 – sildenafil for treatment of erectile dysfunction  
 IND 64924 – sildenafil for treatment of pulmonary arterial hypertension  
 IND 63175 – sildenafil for treatment of pediatric pulmonary arterial hypertension

## 2.3 Drug Formulation

Dry powder blend for constitution with 90 mL water to create approximately 112 mL oral suspension with a drug concentration of 10 mg/mL (based on a stoichiometric potency factor of (b) (4) for citrate salt).

Sildenafil citrate (b) (4); sorbitol (b) (4); citric acid anhydrous (b) (4); sucralose (b) (4); (b) (4) sodium citrate dihydrate (b) (4); xanthan gum (b) (4); (b) (4) grape flavor flavor (b) (4); titanium dioxide (b) (4); sodium benzoate (b) (4); (b) (4) colloidal silicon dioxide anhydrous (b) (4)

## 2.4 Comments on Novel Excipients

None.

## 2.5 Comments on Impurities/Degradants of Concern

None.

## 2.6 Proposed Clinical Population and Dosing Regimen

Children ages 1-17 years with pulmonary arterial hypertension. (b) (4)

## 2.7 Regulatory Background

The original NDA for Revatio (sildenafil) was submitted to the FDA on December 3, 2004 and approved for marketing on 03 June 3, 2005 (NDA 21-845). The approved indication is for the treatment of adults with pulmonary arterial hypertension (PAH). The current application is for the use of REVATIO for the treatment of pediatric patients with PAH (WHO Group I) to improve exercise ability [REDACTED] (b) (4). This application presents data on the powder for oral suspension formulation for those children unable to take sildenafil tablets.

## 3 Studies Submitted

No new nonclinical studies were submitted with this NDA. The in-vitro and in-vivo nonclinical studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction) and for NDA 21845 (for treatment of pulmonary hypertension in adults).

### 3.1 Studies Reviewed

N/A

### 3.2 Studies Not Reviewed

N/A

### 3.3 Previous Reviews Referenced

NDA 20895 – sildenafil for treatment of erectile dysfunction

NDA 21845 – sildenafil for treatment of pulmonary hypertension in adults

## 4 Pharmacology

The in-vitro and in-vivo pharmacology studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction) and for NDA 21845 (for treatment of pulmonary hypertension in adults). No new pharmacology studies were submitted with this NDA.

### 4.1 Primary Pharmacology

Sildenafil selectively inhibits cyclic GMP (cGMP) phosphodiesterase 5 (PDE5). PDE5 is found in virtually all organs and tissues.<sup>1</sup> Prominent effects of PDE5 inhibition include dilation of vascular and visceral smooth muscle and inhibition of platelet aggregation. PDE5 degrades cGMP. Among other roles, cGMP activates protein kinase G, which mediates smooth muscle relaxation, including vasodilation of the pulmonary vasculature. The intrinsic vasodilators, nitric oxide and atrial natriuretic factor, produce vasodilation by increasing cGMP synthesis. PDE5 inhibits vasodilation by degrading cGMP, while sildenafil promotes vasodilation by reducing cGMP degradation.

In NDA 21845 the sponsor reported one in-vivo study (reviewed for NDA 21845) that evaluated the pulmonary and systemic hemodynamic effects of intravenous sildenafil in

an anesthetized, hypoxic dog model. The male and female beagle dogs used in the study weighed from 11-14 kg, but ages were not specified. This appears to be the only pharmacology study reported by that sponsor that was specifically designed to support a pulmonary hypertension indication. Among other findings, that study demonstrated that sildenafil infusion produced much greater decreases in pulmonary vascular resistance and in pulmonary artery pressure than in systemic vascular resistance or systemic arterial pressure.

The sponsor has not reported in-vitro or in-vivo studies that were specifically designed to evaluate pulmonary vascular effects of sildenafil in neonatal or pediatric animals.

There is some data available regarding PDE5 expression and activity in the lungs and/or pulmonary vasculature of neonatal animals. One study reported that PDE5 activity, protein expression and mRNA decreased in mice and lambs during the first hour following birth (a period during which pulmonary vascular resistance decreases), then increased during the first week of life.<sup>2</sup> A second study similarly reported that PDE5 activity and protein expression in the pulmonary arteries of piglets both increased between the first day of life (3-18 hours) and two weeks of age.<sup>3</sup> The results of these studies suggest the possibility that lower doses of sildenafil (or of nitric oxide) might be sufficient to produce pulmonary vasodilation in normal infants during the first day of life (when PDE5 levels are low) than would be true several days later. It is possible, but unproven, that PDE5 expression and activity might undergo similar changes during the first few days of life in animals (or in human neonates) affected by pulmonary artery hypertension.

Published studies have shown that sildenafil delivered orally, intravenously or via nebulization acutely reduces pulmonary vascular resistance in young animals in which acute pulmonary hypertension had been induced.<sup>4,5,6</sup> None of these publications compared required drug doses or magnitude of pharmacodynamic effects for the young animals versus adults of the same species. No studies were identified that evaluated longer-term therapy with sildenafil in neonatal or pediatric animal models of pulmonary hypertension.

## 4.2 Secondary Pharmacology

The FDA Medical Officer who reviewed this NDA has indicated that the pediatric clinical studies submitted with this NDA demonstrate a late, dose-related increase in mortality among patients who participated in a long-term extension study following participation in a sixteen-week, randomized, placebo-controlled trial. The Medical Officer indicated that majority of deaths appear to be the result of worsening pulmonary hypertension, cardiac failure, cardiogenic shock, and ventricular fibrillation, which are expected modes of death in this patient population.

The adverse effect on mortality was unexpected. Increased mortality had not previously been reported for adult or pediatric pulmonary artery hypertension (PAH) patients treated with sildenafil, including the adult PAH patients studied for NDA 21845. The animal studies of sildenafil submitted by the sponsor with NDAs 20895 and 21845 found

large safety margins in the healthy animals (mice, rats and dogs) used in the safety pharmacology and toxicology studies completed for this drug. None of the animal studies submitted by the sponsor suggested that treatment with sildenafil might adversely affect pulmonary or cardiac function in patients with PAH.

A consideration of mechanisms that might contribute to increased cardiac and/or pulmonary mortality was requested. Two hypotheses are discussed below: 1) adverse cardiac effects secondary to a cardiac inotropic effect, possibly mediated by increased levels of cAMP, and 2) dilation of regional pulmonary vasculature that should be constricted by hypoxia, potentially promoting intra-pulmonary shunting and/or ventilation-perfusion mismatch. Both are very preliminary hypotheses. At this point, neither hypothesis explains why outcomes might be different for pediatric PAH patients versus adult PAH patients. The concept that sildenafil therapy could promote intra-pulmonary shunting or ventilation-perfusion mismatch is not new and, thus, might be more likely to have been recognized, if it occurs in children with PAH. The research which indicates sildenafil can increase contractility in failing or hypertrophied right ventricles is recent and may not have been considered by PAH researchers.

Recent publications suggest the possibility that chronic sildenafil treatment could increase right ventricular contractility in patients with PAH and right ventricular hypertrophy or failure. Although Section 2.4.2.2.1 of this NDA states that PDE5 is not found in the heart, a majority of studies that evaluated cardiac tissue from normal animals or human subjects identified PDE5 expression in cardiac tissue.<sup>1</sup> More importantly, PDE5 expression is upregulated in left and right ventricular tissues from failing human hearts and in ventricles exposed to pressure overload.<sup>7,8,9,10,11,12</sup> Of note, one of the cited publications includes a finding of increased PDE5 expression in the right ventricles of neonates and young children with congenital heart anomalies, a patient population that was represented in the clinical trials reported with this NDA.<sup>7</sup>

Upregulation of PDE5 in failing or hypertrophied ventricles is potentially important for PAH patients because it has recently been shown that treatment with sildenafil or with MY-5445, another PDE5 inhibitor, can markedly increase contractility in failing or hypertrophied right ventricles. Two studies have shown that treatment with sildenafil or with MY-5445 increased contractility in right ventricles from rats in whom right ventricular hypertrophy was produced by pulmonary artery banding or by monocrotaline injection, but did not affect contractility in right ventricles from normal rats.<sup>7,13</sup> Similarly, treatment with MY-5445 increased contractility in right ventricular trabeculae obtained from failing human hearts but did not affect contractility in right ventricular trabeculae obtained from normal human hearts.<sup>8</sup>

One mechanism by which sildenafil might increase right ventricular contractility is by indirectly increasing myocyte levels of cAMP. As noted previously, sildenafil inhibits PDE5, reducing degradation of cGMP by PDE5 and increasing tissue levels of cGMP. One effect of cGMP is inhibition of PDE3, which, in turn, reduces degradation of cAMP by PDE3, thus increasing tissue levels of cAMP. One of the studies of right ventricular hypertrophy in rats cited above produced multiple lines of evidence that the increased

contractility produced by PDE5 inhibition was due to increased levels of cAMP and its downstream effector, protein kinase A.<sup>7</sup>

Although increased right ventricular contractility might be expected to produce symptomatic benefit in patients with PAH and right heart failure, there is also a potential for adverse effects. Increased cardiomyocyte levels of cAMP underlie the cardiac contractility effects produced by many inotropic drugs, including the PDE3 inhibitor, milrinone, and the  $\beta$  adrenergic agonist, dobutamine. Treatment of heart failure with inotropic drugs, including milrinone and dobutamine, is associated with an increased risk of ventricular arrhythmia and sudden death and with disease progression.<sup>14,15,16</sup> Exposure of cardiac myocytes to high levels of cAMP (or to various inotropic drugs) has also been shown to induce cardiac myocyte apoptosis, which is believed to contribute to worsening heart failure.<sup>17,18,19,20,21</sup> Studies that examined the adverse effects of inotropic therapy have primarily focused on left ventricular failure, but it is reasonable to suspect that increased inotropy caused by increased cAMP could produce similar adverse effects in the failing right ventricle of a child with PAH.

A second hypothesis regarding the dose-related mortality observed during clinical studies relates to the possibility that sildenafil therapy might inappropriately dilate regional pulmonary blood vessels that should be constricted by hypoxia. The principal concern is that treatment with sildenafil could promote intrapulmonary shunting or ventilation-perfusion mismatch, resulting in reduced oxygen uptake by the blood. Increased intrapulmonary shunting has been reported following sildenafil treatment in normal swine, in swine with meconium-induced pulmonary hypertension, in children with congenital heart disease and increased pulmonary artery pressure, and in an adult with idiopathic pulmonary artery hypertension.<sup>22,23,24,25,26</sup> A bout of pneumonia is one example of a situation where a child with PAH might be particularly susceptible to clinically significant shunting sufficient to reduce blood oxygenation. Although the disease pathophysiology is not identical, it is worth noting that sildenafil treatment has been shown to increase ventilation-perfusion mismatch and to reduce oxygen uptake in patients with chronic obstructive pulmonary disease.<sup>27,28</sup> Finally, although probably less likely than effects on shunting or ventilation-perfusion mismatch, a sufficiently high dose of sildenafil might dilate the ductus arteriosus, producing or worsening a left-to-right shunt. I found one in-vitro study that reports dilation of the ductus by sildenafil, but I could not find in-vivo studies or clinical reports that support the finding.<sup>29</sup>

One adverse effect that is included in the proposed sildenafil label and that was discussed during the review process for this NDA deserves brief mention. The label currently indicates that side effects can include, "heart attack, stroke, irregular heartbeats, and death". Although repeated analyses have found no increased risk of stroke or myocardial infarction associated with sildenafil treatment, there remain occasional case reports that seem to indicate an association, including cases where individuals have suffered repeated ischemic strokes following doses of sildenafil or of other PDE5 inhibitors that were widely separated in time.<sup>30</sup> Although it is well established that PDE5 inhibition inhibits platelet aggregation, a frequently-cited study reported that treatment of platelets with sildenafil instead produced a biphasic response,

consisting of an initial increase in platelet aggregation followed by prolonged inhibition of platelet aggregation.<sup>31,32</sup> Examination of the evidence for a possible stimulatory effect on platelet aggregation indicates that other groups were unable to replicate this result.<sup>33,34</sup> The general opinion among platelet researchers appears to be that PDE5 inhibition (with cGMP upregulation) does not stimulate platelet aggregation.<sup>31,35</sup>

### **4.3 Safety Pharmacology**

The safety pharmacology studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction) and for NDA 21845 (for treatment of pulmonary hypertension in adults). No new safety pharmacology studies were submitted with this NDA.

The previously-reviewed safety pharmacology and in-vivo toxicology studies do not suggest a cardiac or respiratory mechanism that is likely to have caused the dose-related increase in mortality that was observed during the clinical studies reviewed for this NDA. The nonclinical review for NDA 20895 does not mention evaluation of respiratory effects within the safety pharmacology section, but it also does not mention any adverse respiratory effects observed during in-vivo toxicology studies. The most consistent cardiovascular effects noted during safety pharmacology studies were modest reductions in systemic arterial pressure with concomitant (apparently compensatory) increases in heart rate.

Evaluation of hERG channel blockade is not reported in the nonclinical reviews for NDAs 20895 or 21845, but the review for NDA 20895 indicates that an oral dose of 3 mg/kg did not increase QTc in conscious dogs. A published study of the QT interval effects of sildenafil in healthy, adult volunteers reported small increases in QTcF (6 and 9 msec, respectively) following therapeutic (50 mg) and supratherapeutic (400 mg) oral doses of sildenafil.<sup>36</sup>

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **5.1 PK/ADME**

The nonclinical pharmacokinetic studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction). No new nonclinical pharmacokinetic studies were submitted with this NDA.

### **5.2 Toxicokinetics**

The nonclinical toxicokinetic studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction). No new nonclinical toxicokinetic studies were submitted with this NDA.

## **6 General Toxicology**

The single- and repeat-dose toxicology studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction). No new general toxicology studies were submitted with this NDA.

The only example of severe toxicity identified during repeat-dose toxicology studies (including carcinogenicity studies) was death in mice secondary to gastrointestinal dilation. These findings were presumably due to visceral muscle relaxation produced by sildenafil treatment, they were not observed in other species, and they would not appear to be relevant to the cardiac- and pulmonary-related deaths observed during the clinical trials reported with this NDA.

## **7 Genetic Toxicology**

The genetic toxicology studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction). No new genetic toxicology studies were submitted with this NDA.

## **8 Carcinogenicity**

The carcinogenicity studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction).

## **9 Reproductive and Developmental Toxicology**

The reproductive toxicology studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction).

## **10 Special Toxicology Studies**

No new toxicology studies were submitted with this NDA.

## 11 Integrated Summary and Safety Evaluation

Sildenafil selectively inhibits cyclic GMP (cGMP) phosphodiesterase 5 (PDE5). Prominent effects of PDE5 inhibition include dilation of vascular and visceral smooth muscle and inhibition of platelet aggregation. Sildenafil is currently approved for treatment of erectile dysfunction and for treatment of pulmonary arterial hypertension in adults.

No new nonclinical pharmacology, pharmacokinetic or toxicology studies were reported with this NDA. The nonclinical studies of sildenafil reported by the sponsor were previously reviewed for NDA 20895 (for treatment of erectile dysfunction) and for NDA 21845 (for treatment of pulmonary hypertension in adults).

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The FDA Medical Officer who reviewed this NDA indicated that the pediatric clinical studies submitted with this NDA demonstrate a late, dose-related increase in mortality among patients who participated in a long-term extension study following participation in a sixteen-week, randomized, placebo-controlled trial. The majority of deaths appear to be the result of worsening pulmonary hypertension, cardiac failure, cardiogenic shock, and ventricular fibrillation, which are expected modes of death in this patient population.

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None of the animal studies submitted by the sponsor suggested that treatment with sildenafil might adversely affect pulmonary or cardiac function in patients with PAH. The only example of severe toxicity identified during repeat-dose toxicology studies (including carcinogenicity studies) was death in mice secondary to gastrointestinal dilation. These findings were presumably due to visceral muscle relaxation produced by sildenafil treatment, they were not observed in other species, and they would not appear

to be relevant to the cardiac- and pulmonary-related deaths observed during the clinical trials reported with this NDA.

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There are no nonclinical findings that would prevent approval of this NDA. The NDA is approvable from a nonclinical standpoint. However, the lack of significant nonclinical safety signals does not ameliorate the adverse clinical outcomes observed in the clinical studies reported with this NDA.

There are no additional nonclinical recommendations. However, if future clinical study requests are made to the sponsor that relate to pulmonary artery hypertension indications (adult or pediatric), it could be suggested that future clinical studies include: 1) evaluation of the possibility that sildenafil treatment might produce right ventricular inotropic effects, particularly at timepoints when right ventricular hypertrophy or failure is present (and when PDE5 levels in the right ventricle might be upregulated), and 2) evaluation of the possibility that sildenafil treatment might promote adverse intra-pulmonary shunting and/or ventilation-perfusion mismatch, including during bouts of pneumonia.

## 12 References

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1. Lin CS, et al. Expression, distribution and regulation of phosphodiesterase 5. *Curr Pharm Des.* 2006;12(27):3439-57.
2. Hanson KA, et al. Developmental changes in lung cGMP phosphodiesterase-5 activity, protein, and message. *Am J Respir Crit Care Med.* 1998;158(1):279-88.
3. Moreno L, et al. Postnatal maturation of phosphodiesterase 5 (PDE5) in piglet pulmonary arteries: activity, expression, effects of PDE5 inhibitors, and role of the nitric oxide/cyclic GMP pathway. *Pediatr Res.* 2004;56(4):563-70.
4. Weimann J, et al. Sildenafil is a pulmonary idiopathic pulmonary arterial hypertension in children and vasodilator in awake lambs with acute pulmonary hypertension. *Anesthesiology.* 2000;92(6):1702-12.
5. Ichinose F, et al. Nebulized sildenafil is a selective pulmonary vasodilator in lambs with acute pulmonary hypertension. *Crit Care Med.* 2001;29(5):1000-5.
6. Shekerdemian LS, et al. Intravenous sildenafil lowers pulmonary vascular resistance in a model of neonatal pulmonary hypertension. *Am J Respir Crit Care Med.* 2002;165(8):1098-102.
7. Nagendran J, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. *Circulation.* 2007;116(3):238-48.
8. Shan X, et al. Differential Expression of PDE5 in Failing and Nonfailing Human Myocardium. *Circ Heart Fail.* 2012;5(1):79-86.
9. Pokreisz P, et al. Ventricular phosphodiesterase-5 expression is increased in patients with advanced heart failure and contributes to adverse ventricular remodeling after myocardial infarction in mice. *Circulation.* 2009;119(3):408-16.
10. Lu Z, et al. Oxidative stress regulates left ventricular PDE5 expression in the failing heart. *Circulation.* 2010;121(13):1474-83.
11. Johnson WB, et al. Profiling of cAMP and cGMP phosphodiesterases in isolated ventricular cardiomyocytes from human hearts: comparison with rat and guinea pig. *Life Sci.* 2012;90(9-10):328-36.
12. Takimoto E, et al. Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy. *Nat Med.* 2005;11(2):214-22.
13. Andersen A, et al. Effects of phosphodiesterase-5 inhibition by sildenafil in the pressure overloaded right heart. *Eur J Heart Fail.* 2008;10(12):1158-65.
14. Packer M, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med.* 1991;325(21):1468-75.
15. Cohn JN, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med.* 1998;339(25):1810-6.
16. O'Connor CM, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J.* 1999;138(1 Pt 1):78-86.
17. Mann DL, et al. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation.* 1992;85(2):790-804.
18. Iwai-Kanai E, et al. alpha- and beta-adrenergic pathways differentially regulate cell type-specific apoptosis in rat cardiac myocytes. *Circulation.* 1999;100(3):305-11.

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19. Singh K, et al. Adrenergic regulation of cardiac myocyte apoptosis. *J Cell Physiol.* 2001;189(3):257-65.
  20. Zhu WZ, et al. Linkage of beta1-adrenergic stimulation to apoptotic heart cell death through protein kinase A-independent activation of Ca<sup>2+</sup>/calmodulin kinase II. *J Clin Invest.* 2003;111(5):617-25.
  21. Burniston JG, et al. Relative toxicity of cardiotoxic agents: some induce more cardiac and skeletal myocyte apoptosis and necrosis in vivo than others. *Cardiovasc Toxicol.* 2005;5(4):355-64.
  22. Kleinsasser A, et al. Sildenafil modulates hemodynamics and pulmonary gas exchange. *Am J Respir Crit Care Med.* 2001;163(2):339-43.
  23. Shekerdemian LS, et al. Interaction between inhaled nitric oxide and intravenous sildenafil in a porcine model of meconium aspiration syndrome. *Pediatr Res.* 2004;55(3):413-8.
  24. Ryhammer PK, et al. Effect of intravenous sildenafil on pulmonary hemodynamics and gas exchange in the presence and absence of acute lung injury in piglets. *Pediatr Res.* 2006;59(6):762-6.
  25. Schulze-Neick I, et al. Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. *Circulation.* 2003;108 Suppl 1:II167-73.
  26. Castro PF, et al. Intrapulmonary shunting associated with sildenafil treatment in a patient with idiopathic pulmonary arterial hypertension. *Thorax.* 2011;66(12):1097-8.
  27. Blanco I, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med.* 2010;181(3):270-8.
  28. Lederer DJ, et al. Sildenafil for Chronic Obstructive Pulmonary Disease: A Randomized Crossover Trial. *COPD.* 2012 Feb 23. [Epub ahead of print]
  29. Thébaud B, et al. Sildenafil reverses O<sub>2</sub> constriction of the rabbit ductus arteriosus by inhibiting type 5 phosphodiesterase and activating BK(Ca) channels. *Pediatr Res.* 2002;52(1):19-24.
  30. Stefanović-Budimkić M, et al. Recurrent ischemic stroke associated with sildenafil and tadalafil use in a young adult. *Clin Neurol Neurosurg.* 2012;114(4):405-7.
  31. Smolenski A. Novel roles of cAMP/cGMP-dependent signaling in platelets. *J Thromb Haemost.* 2012;10(2):167-76.
  32. Li Z, et al. A stimulatory role for cGMP-dependent protein kinase in platelet activation. *Cell.* 2003;112(1):77-86.
  33. Gambaryan S, et al. Potent inhibition of human platelets by cGMP analogs independent of cGMP-dependent protein kinase. *Blood.* 2004;103(7):2593-600.
  34. Marshall SJ, et al. GPIIb-dependent platelet activation is dependent on Src kinases but not MAP kinase or cGMP-dependent kinase. *Blood.* 2004;103(7):2601-9.
  35. Siess W. Does cGMP mediate platelet inhibition or stimulation? *Blood.* 2004;103(7):2435-7.
  36. Morganroth J, et al. Evaluation of vardenafil and sildenafil on cardiac repolarization. *Am J Cardiol.* 2004;93(11):1378-83.

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/s/  
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DONALD N JENSEN  
05/01/2012

THOMAS PAPOIAN  
05/01/2012  
I concur.