CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

PHARMACOLOGY REVIEW(S)

NDA #22-473

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Revatio™ (Sildenafil Citrate) ——— Injection b(4)

Applicant:
Pfizer, Inc., New York, NY

Reviewer:
Thomas Papoian, Ph.D., D.A.B.T.

Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration

February 24, 2009

PHARMACOLOGY AND TOXICOLOGY REVIEW

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1. EXECUTIVE SUMMARY

1.1. SUBMISSION BACKGROUND

Oral administration of sildenafil citrate has been approved previously for the indications of male erectile dysfunction (Viagra®; NDA #20-895) and pulmonary hypertension (Revatio®; NDA #21-845). The current application (NDA #22-473) is to gain approval of Revatio® (sildenafil citrate) for intravenous (i.v.) use in adult patients with pulmonary arterial hypertension (PAH) who are temporarily unable to take oral medication, and for whom the physician believes continuity of treatment is in the patient's best interest. This application represents a new pharmaceutical formulation, strength, and route of administration for sildenafil citrate. According to the sponsor, an i.v. dose of 10 mg t.i.d. (i.e., 3X/day) over 5 min to humans is projected to produce a similar AUC (i.e., systemic exposure) to that following the recommended therapeutic oral dose of 20 mg t.i.d.

Although no new pharmacology or toxicology studies were conducted or submitted with this application, previous nonclinical studies submitted in support of NDAs #20-895 (Viagra®) and #21-845 (Revatio®) were used to support the safety of the new i.v. formulation.

1.2. RECOMMENDATIONS

1.1.1. Recommendation on Approvability

Approvable

1.1.2. Recommendations for Additional Nonclinical Studies

None

1.1.3. Recommendations on Labeling

None

1.3. BRIEF SUMMARY OF NONCLINICAL FINDINGS

1.2.1. Pharmacological Activity

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 (PDE5), which is the enzyme responsible for degradation of intracellular cGMP. The resulting increase in cGMP levels produces vascular smooth muscle relaxation and vasodilatation. In the case of producing erection, sexual stimulation causes local release of nitric oxide (NO). Inhibition of PDE5 by sildenafil causes less degradation and increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. In the case of reducing pulmonary hypertension, sildenafil inhibits the degradation of cGMP by PDE5 in the smooth muscle of the pulmonary vasculature, resulting in relaxation and vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

1.2.2. Toxicological Findings

No new toxicology studies were conducted or submitted since the original Viagra® submission (NDA #20-895). However, in that previous submission one month toxicity studies in rats and dogs using the i.v. route of administration were conducted with sildenafil (UK-92,480). Also, an intra-arterial irritation study was conducted in rabbits.
The results are summarized as follows:

- In the one month i.v. toxicity study in rats using doses up to 4 mg/kg/day, the only noticeable finding was a chronic inflammation in the myocardium (left and right ventricles). Although this lesion was found in controls, the incidence in the high-dose males was about twice as high as that found in controls. The significance of these findings was not clear to the sponsor, and cannot be explained by the known pharmacological properties of the drug. It should be noted that myocardial inflammation was not seen in the repeat-dose (4-week and 6-month) rat toxicity studies conducted by the oral route of administration. When based on surface area, the NOAEL dose in rats (i.e., 4 mg/kg/day) represents about **1X**, or equal to, the human dose of 10 mg t.i.d. (= 30 mg/day). However, when based on "projected" Cmax values calculated by the sponsor, the rat NOAEL dose represents **28.6X** the single human dose of 10 mg.

- In the one month i.v. toxicity study in beagle dogs, no evidence of toxicity was seen when sildenafil was given i.v. at doses up to 4 mg/kg/day. When based on surface area, the NOAEL dose in dogs (i.e., 4 mg/kg/day) represents about **4X** the human dose of 10 mg t.i.d. (= 30 mg/day). However, when based on "projected" Cmax values calculated by the sponsor, the dog NOAEL dose represents **28.6X** the single human dose of 10 mg.

- Administration of a single 0.5 ml intra-arterial injection of sildenafil at a concentration of 2 mg/ml into the ears of rabbits did not increase the incidence or severity of any lesions from that seen in vehicle control-treated rabbits. The concentration of sildenafil used in this study (2 mg/ml) was **2.5X** the concentration proposed for intravenous use in humans (0.8 mg/ml).

1.2.3. Nonclinical Safety Issues Relevant for Clinical Use

No new safety issues have been identified in the current submission that were not previously addressed in NDAs #20-895 (Viagra) and #21-845 (Revatio).

2. PHARMACOLOGY AND TOXICOLOGY REVIEW

2.1. BASIC INFORMATION

NDA # 22-473
Submission Date: Dec. 16, 2008
Sponsor: Pfizer, Inc., New York, NY

Drug Substance:

Trade Name: Revatio® (Sildenafil Citrate)————— Injection b(4)

Generic Name: Sildenafil citrate

Code Names: UK-92,480

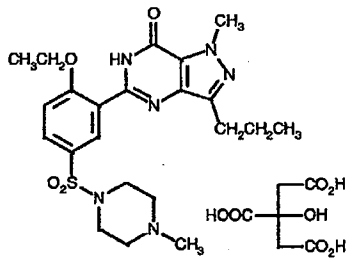
Chemical Name: 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine citrate salt

CAS Registry Number: 171,599-83-0

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

Molecular Weight: 666.7 (citrate salt)

Structure:



Related INDs/NDAs: IND #46,863 (Viagra); NDA #20-895(Viagra); NDA #21-845 (Revatio)

Pharmacological Class: Cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) inhibitor.

Clinical Indication: Pulmonary arterial hypertension (PAH)

Formulation (Drug Product): The new i.v. formulation is a solution of 0.8 mg sildenafil citrate per ml in an aqueous solution of 5.05% w/v glucose (dextrose), and will be provided as a sterile, single-use, ready-to-use injectable solution in a [redacted] vial. The composition of the drug product is shown as follows. b(4)

Composition of Drug Product

Component	Function	Reference to Standards	Composition (mg/mL)	Unit Formula (mg [redacted] vial)
Sildenafil Citrate, for parenteral use	Active	Pfizer	1.124[u]	[redacted]
Dextrose[v]	[redacted]	USP, Ph.Eur.	50.5000[w]	
Water for Injection	[redacted]	USP, Ph.Eur.	[redacted]	
[redacted]	[redacted]	USP, Ph.Eur.	[redacted]	[redacted]
TOTAL				

b(4)

b(4)

[u] Equivalent to 0.8 mg/mL of sildenafil, based on a stoichiometric potency factor of [redacted] for [redacted]. Actual weight may vary according to the potency of lot used.

[v] Either dextrose [redacted] or dextrose [redacted] may be used. Also known as glucose.

[w] Reflects [redacted] dextrose quantity.

[x] [redacted]

[y] Based on [redacted]

[z] [redacted]

b(4)

b(4)

Route Of Administration: Intravenous (i.v.)

2.2. PHARMACOLOGY

No new pharmacology studies were submitted.

2.3. TOXICOLOGY

No new toxicology studies were conducted or submitted since the original Viagra® submission (NDA #20-895). However, in that previous submission one month toxicity studies in rats and dogs using the i.v. route of administration were conducted with sildenafil (UK-92,480). Also, an intra-arterial irritation study was conducted in rabbits. The results are summarized below (also see Pharm/Tox review dated Jan. 23, 1998).

2.3.1. One Month Intravenous Toxicity Study in Rats

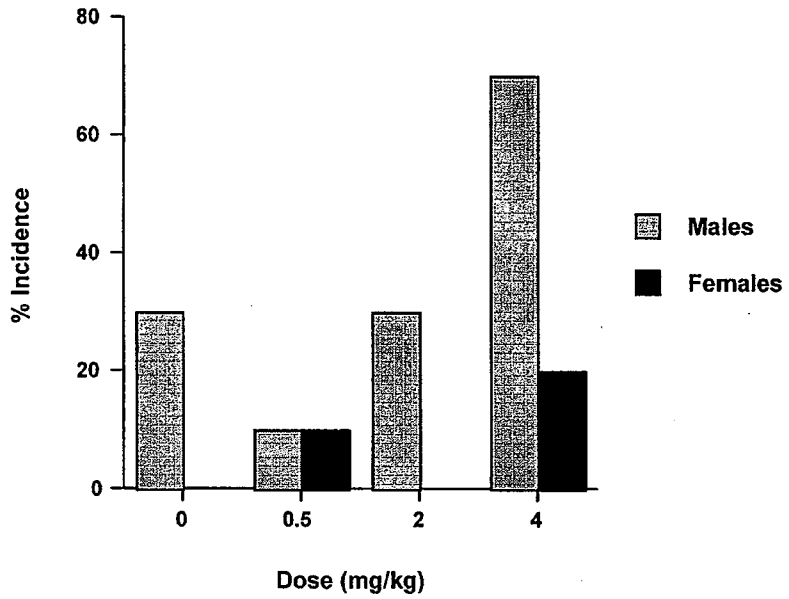
Testing Facility: Laboratoires Pfizer; Centre de Recherche; Ambroise Cedex; France
Study Number: 91044
Study Date(s): 3/29/91 to 4/25/91
GLP Compliance: Yes

Male and female Sprague-Dawley rats (10/sex/group; 267 gms for males and 187 gms for females) were injected with UK-92,480 (lot no. 953-27) i.v. at 0.5, 2, or 4 mg/kg/day for 28 days. Controls received vehicle (5% mannitol solution). Rats were observed for clinical signs and weighed once per week. An ophthalmological exam was performed before and at the end of treatment. One day after the last dose, blood was taken for hematology and clinical chemistry. Urine was collected for urinalysis. Rats were then sacrificed and a necropsy performed which included a gross exam. Weights of several organs were taken. Microscopic exam of 34 tissues was performed.

No deaths were reported. The only noticeable finding was a chronic inflammation in the myocardium (left and right ventricles). Although this lesion was found in controls, the incidence in the high-dose males was about twice as high as that found in controls (Figure 1). The significance of these findings was not clear to the sponsor, and cannot be explained by the known pharmacological properties of the drug. It should be noted that myocardial inflammation was not seen in the repeat-dose (4-week and 6-month) rat toxicity studies conducted by the oral route of administration.

Figure 1

Percent Incidence of Myocardial Chronic Inflammation in Rats Treated with UK-92,480



2.3.2. One Month Intravenous Toxicity Study in Dogs

Testing Facility: Laboratoires Pfizer; Centre de Recherche; Ambroise Cedex; France
Study Number: 91041
Study Date(s): 4/4/91 to 5/2/91
GLP Compliance: Yes

Male and female beagle dogs (3/sex/group; 9.5 kg for males and 8.5 kg for females) were injected with UK-92,480 (lot no. 953-27) i.v. at 0.5, 4, or 4 mg/kg/day for 28 days. Controls received vehicle (5% mannitol solution). Dogs were observed for clinical signs. Pupil size and pupillary reflex to light was performed before and at the end of treatment. Body weights were recorded weekly. ECGs, systolic blood pressure, and heart rates were recorded periodically before and two hours after dosing. Blood was sampled before treatment and after 13 and 28 days of treatment for clinical chemistry and hematology. Urine was collected before and at the end of treatment for urinalysis. One day after the last dose, dogs were sacrificed and a necropsy performed which consisted of a gross exam, weighing of several organs, and microscopic exam of 35 tissues.

No deaths were reported. Clinical signs consisting of emesis and salivation were unrelated to treatment. No effects were reported on pupil size or pupillary reflex to light. There were no drug-related effects on cardiovascular parameters (ECG, BP, HR). No other drug-related effects were noted.

It was concluded that UK-92,480 given to dogs i.v. at up to 4 mg/kg/day for 28 days produced no evidence of toxicity.

2.3.3. Intra-Arterial Irritation Study in Rabbits

Two groups of 4 female New Zealand white rabbits (3.363 kg ± 0.245 kg) received on Day 1 of study a single injection of 0 (vehicle - aqueous solution containing 5% mannitol) or 1 mg of UK-92,480-10 in 0.5 ml into the median artery of the left ear. The animals were examined daily for clinical signs and their food consumption was evaluated.

The injection site and the corresponding area of the right ear were examined 1, 3 and 5 hours post dosing on Day 1, then once a day up to sacrifice. Body weight was recorded weekly. Two animals of each of the control and treated groups were sacrificed on Day 3. The other animals were sacrificed on Day 21. The injection sites and corresponding areas of the right ear were sampled for histopathological examination.

All the animals survived throughout the study. Hematoma or redness around the site of injection were seen in all the treated and control animals. In both groups the changes disappeared within 4 to 6 days. No other clinical signs were observed.

No remarkable effects of treatment were reported on food consumption or body weight.

Necropsy findings did not show any remarkable changes.

Microscopic examination found peri-arterial hemorrhage and acute inflammation at Day 3, while a few peri-arterial hemosiderin laden macrophages were the only indicator of the administration at Day 21. These changes were recorded with similar incidence and severity in control and treated groups. No other lesions were considered to be related to the injection.

It was concluded that administration of a single intra-arterial injection of sildenafil at 2 mg/ml into the ears of rabbits did not increase the incidence or severity of any lesions from that seen in vehicle control-treated rabbits. The concentration of sildenafil used in this study (2 mg/ml) was **2.5X** the concentration proposed for intravenous use in humans (0.8 mg/ml).

2.4. INTEGRATED SUMMARY AND EVALUATION

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 (PDE5), which is the enzyme responsible for degradation of cGMP. Increased cGMP levels result in vascular smooth muscle relaxation and vasodilatation. In the case of reducing pulmonary hypertension, sildenafil inhibits the degradation of cGMP by PDE5 in the smooth muscle of the pulmonary vasculature, resulting in relaxation and vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

The current application (NDA #22-473) is to gain approval of Revatio (sildenafil citrate) for intravenous use in adult patients with pulmonary arterial hypertension who are temporarily unable to take oral medication, and for whom the physician believes continuity of treatment is in the patient's best interest. This application represents a new pharmaceutical formulation, strength, and route of administration for sildenafil citrate. According to the sponsor, an i.v. dose of 10 mg t.i.d. over 5 min to humans is projected to produce a similar systemic exposure (i.e., AUC) to that following the recommended therapeutic oral dose of 20 mg t.i.d.

Although no new toxicology studies were conducted or submitted since the original Viagra submission (NDA #20-895), one month toxicity studies in rats and dogs using the i.v. route of administration were conducted with sildenafil as part of the original Viagra submission. Also, an intra-arterial irritation study was conducted in rabbits. These studies, together with i.v. studies conducted in humans as part of the clinical development for Viagra, are being referenced to support the safety of Revatio for short-term i.v. use.

In the one month i.v. toxicity study in rats using doses up to 4 mg/kg/day, the only noticeable finding was a chronic inflammation in the myocardium (left and right ventricles). Although this lesion was found in controls, the incidence in the high-dose males was about twice as high as that found in controls. The significance of these findings was not clear to the sponsor, and cannot be explained by the known pharmacological properties of the drug. It should be noted that myocardial inflammation was not seen in the repeat-dose (4-week and 6-month) rat toxicity studies conducted by the oral route of administration.

In the one month i.v. toxicity study in beagle dogs, no evidence of toxicity was seen when sildenafil was given i.v. at doses up to 4 mg/kg/day.

Administration of a single 0.5 ml intra-arterial injection of sildenafil at a concentration of 2 mg/ml into the ears of rabbits did not increase the incidence or severity of any lesions from that seen in vehicle control-treated rabbits. The concentration of sildenafil used in this study (2 mg/ml) was **2.5X** the concentration proposed for intravenous use in humans (0.8 mg/ml).

Since toxicokinetic samples were not collected during the one-month i.v. rat and dog toxicity studies, it is not possible to directly compare the exposures seen in animals after i.v. administration to that seen in humans given sildenafil i.v. However, when based on surface area, the NOAEL doses in rats and dogs (i.e., 4 mg/kg/day) represent about **1X** and **4X**, respectively, the human dose of 10 mg t.i.d. (= 30 mg/day), when based on a 60 kg individual (Table 1).

Therefore, the drug exposures seen in animals following i.v. administration were at least equal to or greater than those expected in human subjects following i.v. administration when assessed by standard surface area extrapolations.

Table 1

Comparison of Doses Used in Animals to Doses Proposed for Humans
(Based on Surface Area)

Species	**Dose (mg/kg)**	***km***	**Dose (mg/m^2)**	**Multiple of Human Dose**
Rat	4	6	24	**1X**
Dog	4	20	80	**4X**
Human*	0.5 (10 mg t.i.d.)	37	18.5	--

(* = based on a 60 kg individual)

In their attempt to compare the doses used in animals to those proposed for humans, the sponsor compared Cmax values from i.v. pharmacokinetic studies conducted at the no-observable-adverse-effect level (NOAEL) doses in rats and dogs (4 mg/kg) to human Cmax data following a single 20 mg i.v. infusion over 40 min (= 0.14 mg/kg, when based on a 70 kg individual; from clinical Study #148-203). Values calculated were based on the sum of the unbound fractions of the sildenafil parent (UK-92,480) and active metabolite (UK-103,320). It should be noted that the sponsor assumes that human Cmax values will remain the same between the 5 and 40 min infusions.

Table 2 shows the "projected" Cmax values for the unbound parent (sildenafil) and active metabolite (UK-103,320) at NOAEL doses in rats and dogs and the human "projected" Cmax values following a single i.v. dose over 5 min. The multiples of the Cmax values relative to that projected for humans is shown in Table 3. Based on these calculations, the "projected" Cmax values in rats and dogs were **28.6X** higher than the "projected" human Cmax values following a single dose of 10 mg (= 0.14 mg/kg). Therefore, based on these assumptions for Cmax values, the one-month i.v. toxicity studies conducted in rats and dogs appear to provide an adequate margin of safety to support the i.v. use of sildenafil in humans.

Table 2 (Sponsor's Table)

Table 2. Projected Cmax values for sildenafil and UK-103,320 at NOAELs in toxicology species in comparison with projected human Cmax values following intravenous administration over 5 minutes

Species	Dose[a] (mg/kg)	Total Projected Cmax (ng/mL) [Unbound Projected Cmax (ng/mL)][b]	
		Sildenafil	UK-103,320
Rat (M)	4	2880 [144][c]	147 [16.2][c]
Rat (F)	4	2340 [117][c]	89.9 [9.9][c]
Dog (M and F)[d]	4	1128 [158][e]	72 [10.1][e]
Human	0.14[f]	203 [8.1][g]	13.5 [0.7][h]

M = Male; F = Female.
[a] No observed adverse effect level (NOAEL) dose in 1 month IV toxicology studies.
[b] Rat unbound fraction (fu) of sildenafil is 0.05 and UK-103,320 is 0.11. Dog fu of sildenafil is 0.14 and UK-103,320 is 0.14. Human fu of sildenafil is 0.04 and UK-103,320 is 0.05.
[c] Cmax values used from 4 mg/kg IV dose in rat PK study (previously submitted; VIAGRA NDA 20-895).
[d] Data for male and female animals have been combined for dog since there is no evidence of a gender difference in pharmacokinetics.
[e] Extrapolated Cmax values calculated from Cmax values from 1 mg/kg IV dose in dog PK study (previously submitted; VIAGRA NDA 20-895). Calculations: Sildenafil Cmax: 282 ng/mL multiplied by 4 = 1128. UK-103,320 Cmax: 18 ng/mL multiplied by 4 = 72 ng/mL.
[f] Human dose in mg/kg calculated assuming 70 kg bodyweight (10 mg TID).
[g] Human sildenafil Cmax data projected for 5 minute IV infusion (study report "Two compartmental analysis of pharmacokinetics in Study 148-203").
[h] Human UK-103,320 Cmax data used from study 148-203 assuming that the Cmax remains the same between the 40 and 5 minute infusion.

Table 3 (Sponsor's Table)

Table 3. Dose and unbound Cmax multiples for sildenafil and UK-103,320 based on NOAELs in toxicology species in comparison with projected human data

Species	Dose (mg/kg)	Dose Multiple	Unbound Cmax Multiples	
			Sildenafil	UK-103,320
Rat (M)	4	28.6	18	23
Rat (F)	4	28.6	14	14
Dog (M and F)	4	28.6	20	14
Human projection	0.14	NA	NA	NA

M = Male; F = Female; NA = Not applicable.

In conclusion, intravenous administration of sildenafil to rats and dogs did not produce any toxicities not seen previously with sildenafil given orally.

2.5. Recommendations

Internal: Given the extensive human experience with sildenafil since its initial approval in 1998, and the lack of any unanticipated toxicities in animals following 28 days of intravenous administration at exposures equal to or greater than the anticipated clinical exposure, there are no safety concerns from a pharmacology or toxicology perspective.

In addition, it should be confirmed by the Clinical Pharmacology reviewer that an i.v. dose of 10 mg t.i.d. over 5 min to humans produces a "projected" AUC similar to that seen following the recommended therapeutic oral dose of 20 mg t.i.d.

To the Sponsor: None

Thomas Papoian, Ph.D.
Pharmacologist

Albert DeFelice, Ph.D.
Supervisory Pharmacologist
(*Concurrence*)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Papoian
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PHARMACOLOGIST