Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Section 1, page 1 through Section 6.11, page 24

1. Materials utilized in review

1.1. Materials from NDA/IND

NDA submissions reviewed are listed on the front cover. The material included conventional study reports for a total of 71 clinical studies, most of which are individually reviewed in Appendix A. The sponsor also provided an electronic submission of study documents, all data from major placebo-controlled studies, and page-images of CRFs for deaths and withdrawals for adverse events. These materials were all reviewed.

The clinical development program for sildenafil was undertaken under IND Some clinical study reports and clinical datasets were submitted to the IND in the weeks prior to full NDA submission.

1.2. Related reviews or consults

There are no other drugs of this pharmacological class previously reviewed. The Division has previously reviewed NDA 20-700, transurethral alprostadil for male impotence, and references are made to the clinical review of that NDA, dated 25 June 1996.

1.3. Other resources

An NLM search was conducted to look for publications involving clinical trials of sildenafil. The results of this search are discussed in section 5.2.3 on page 15.

2. Background

2.1. Indication

The proposed indication for sildenafil is for the treatment of male erectile dysfunction.

2.2. Information from related pharmacologically related agents

Sildenafil is a type V phosphodiesterase inhibitor. Other members of the class are under clinical and pre-clinical development. There are no previous NDAs for agents of this class.

2.3. Administrative history

The development program for sildenafil was managed under IND .led in The sponsor has met with DCRDP on several occasions; DCRDP encouraged changing the major efficacy end point to be sexual performance rather than erectile function. There have been no substantive administrative issues.

2.4. Proposed labeling

The proposed label is reviewed in section 9 on page 57.

2.5. Foreign marketing

As of the date of filing, sildenafil was not marketed in any country.

2.6. Other background information

None.

3. Chemistry, manufacturing, and controls[1]

3.1. Basis of review

This section of the review is based upon the Chemistry review dated 15 November 1997. This review is signed by Review Chemist J.V. Advani and Supervisory Chemist R. Wolters.

3.2. Structure

Sildenafil citrate is 1-[4-ethoxy-3-(6, 7-dihydro-1-methyl-7-oxo-3-propyl-1 H-pyrazolo[4,3-d]pyrimidin-5- yl)phenylsulfonyl]-4-methylpiperazine citrate salt, with molecular formula $C_{29}H_{37}O_{11}N_6S$, molecular weight 666.7, and structure as shown in Figure 1 below.

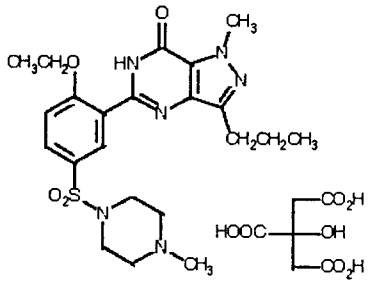

Figure 1. Structure of sildenafil.

3.3. Deficiencies

A small number of minor issues remained at the time of this review, the most notable of which was data to support a 24-month expiration date. Data had been provided in support of a 12-month expiration date.

[1] In some plases, the Chemistry Review refers to sildenafil as UK-92,480.

4. Animal pharmacology[1]

4.1. Basis of review

This section of the review is based upon draft pharmacology review (undated) by Drs. EA Barry, AF DeFelice, and T Papoian, but the interpretations are, unless otherwise noted, those of the clinical reviewers.

4.2. Mechanism of action

The data show that sildenafil is a potent, complete inhibitor of Type V phosphodiesterase. The distribution of various forms of phosphodiesterase and the relative selective selectivity of sildenafil for various forms is shown in Table 1 below.

Table 1. Inhibition of phosphodiesterase forms by sildenafil.

	Source	Mean IC_{50} (nM)		Source	Mean IC_{50} (nM)
PDE1	Human cardiac ventricle	280	PDE5	Human corpora cavernosa	3.5
	Rat kidney	430		Human platelet	6.1
	Rat diaphragm	218		Rabbit platelet	3.9
PDE2	Human corpora cavernosa	68000		Dog platelet	4.8
	Rat kidney	>100000		Rat diaphragm	1.8
	Rat diaphragm	33000			
PDE3	Human corpora cavernosa	16000	PDE6	Human retina—cone	34
	Human platelet	41000		Human retina—rod	38
	Rabbit platelet	48000		Dog retina—cone	27
PDE4	Human skeletal muscle	7200		Dog retina—rod	58
	Rat kidney	19000		Rat retina—cone	27
	Rat diaphragm	6300		Rat retina—rod	67

Sildenafil produced relaxation of corpora cavernosal smooth muscle pre-contracted by electrical stimulation, phenylephrine, or methacholine, in isolated tissues or intact animals. The effect of sildenafil appeared to be mediated by local liberation of nitric oxide, since the effects could be prevented by a nitric oxide synthase inhibitor.

Sildenafil alone had no effect on platelet aggregation, but it potentiated anti-aggregatory or dis-aggregatory effects of the nitric oxide donor, sodium nitroprusside.

4.2.1. Screening for other activities

Sildenafil had no effect on the dose-response curves for contraction of rabbit aorta by phenylephrine, constriction of rabbit coronary arteries by endothelin-1, tension in field-stimulated dog ventricular trabeculae.

Doses above that necessary to affect corpora cavernosa produced blood pressure reductions in spontaneously hypertensive rats.

Sildenafil had no effect on gastrointestinal tone in various mammalian species.

Effects of sildenafil on the electroretinogram in dogs were similar to those seen in humans[2].

Sildenafil displayed little affinity for adenosine A_1, A_{2b}, or A_3 receptors, α- and β-adrenoreceptors, dopamine D_1 or D_2 receptors, histamine H_1, 5-HT_1, 5-HT_2,

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1. In some places, the Pharmacology Review refers to sildenafil as UK-92,480.
2. *Study 148-232: A randomised, double-blind, placebo-controlled, crossover pilot study to investigate the effects of a single oral tablet dose of sildenafil (200mg) on visual function (electroretinogram, photostress, visual field and colour discrimination tests) in healthy male volunteers and patients with diabetic retinopathy.* on page 177.

muscarinic, or opioid receptors, or for verapamil, dihydropyridine, or benzodiazepine binding sites.

In a study lacking a positive control, sildenafil had no effect on defibrillatory threshold in dogs.

Sildenafil was not found to show effects on the central nervous system—sedation, interaction with alcohol or barbiturates, or motor coordination.

Doses of irbesartan several-fold greater than necessary to antagonize angiotensin II receptor-mediated actions failed to produce central or autonomic effects in mice.

4.3. Pharmacokinetics

Single-dose pharmacokinetics are compared across species in Table 2 below, to facilitate interpretation of toxicity findings.

Table 2. Single-dose pharmacokinetics in mammals.

	Mouse	Rat (M)	Rat (F)	Rabbit	Dog	Man
Intravenous						
$t_{1/2}$ (h)	1.3	0.3	1.9	1.8	5.2	4.0
AUC (ng.h/mL/mg)	174	350	1280	—	1550	1990
CL/F (mL/min/kg)	91	48	13	—	12	9.8
V_d (L/kg)	1.0	1.1	2.0	—	5.2	1.5
Free (%)	6	5	5	9	14	4
Oral						
C_{max} (ng/mL/mg)	30	11	147	44	117	245
T_{max} (h)	0.5	1.0	3.0	2.0	1.1	1.5
AUC (ng.h/mL/mg)	31	51	252	190	842	815
Bioavail (%)	17	15	44	—	54	41
Cmax ratio (sildenafil/UK-103-320)	4.8	0.2	5.0	1.9	6.9	2.5

4.4. Toxicology

4.4.1. Genetic toxicity

A standard battery of genetic toxicity studies were performed. The results, discussed in detail in the pharmacologists' review, raise no clinical safety concerns.

4.4.2. Single-dose

Following oral administration, clinical signs were absent from mice and rats given 300 mg/kg. The minimum lethal dose is within an order of magnitude of this level. Intravenous administration was limited by solubility of sildenafil citrate; there were no clinical signs at 20 mg/kg in mice or 10 mg/kg in rats.

4.4.3. Sub-chronic/chronic

4.4.3.1. Oral

4.4.3.1.1. Rats

Ten-day oral exposure up to 500 mg/kg in rats was substantially unremarkable except for hepatic changes consistent with enzyme induction.

Thirty-day oral exposure up to 200 mg/kg in rats showed similar hepatic changes, but also showed testicular atrophy (level of seminiferous tubules; no gross effects) in most animals.

Six-month oral exposure up to 60 mg/kg in rats showed similar hepatic changes. Testicular changes are not mentioned in the review.

4.4.3.1.2. Dogs

Ten-day oral exposure up to 100 mg/kg in dogs showed dose-related decreases in blood pressure and increases in heart rate 2 hours after dosing. Dose-related increases in liver mass were also reported.

One-month oral exposure up to 80 mg/kg in dogs showed similar effects on blood pressure and heart rate.

Six-month oral exposure up to 50 mg/kg in dogs showed dose-related increases in liver mass and coronary periarteritis in the high-dose group.

Twelve-month oral exposure up to 50 mg/kg in dogs showed coronary periarteritis in the high-dose group.

The demonstrated "no-effect level" for periarteritis in these two studies of dogs was about 8 times the maximum recommended dose in man; periarteritis was observed at about 50 times the maximum recommended dose. Periarteritis has been described in animal toxicology studies of other vasodilators, and it is not believed to have any clinical significance.

4.4.3.1.3. Mice

Three-month oral exposure up to 200 mg/kg in mice revealed a minimum lethal dose of 50 mg/kg, with death attributed to gastrointestinal dilation. Increased liver mass was reported in a repeat study.

4.4.3.2. Intravenous

4.4.3.2.1. Rats

Thirteen-day intravenous exposure up to 60 mg/kg in rats showed acute vasodilation, but not other abnormalities were noted.

One-month intravenous exposure up to 4 mg/kg revealed no obviously treatment-related effects.

4.4.3.2.2. Dogs

Fourteen-day intravenous exposure up to 10 mg/kg in dogs showed increased liver mass.

One-month intravenous exposure up to 4 mg/kg in dogs showed no evidence of toxicity.

4.4.4. Chronic

4.4.4.1. Rats

Twenty-four-month oral exposure up to 60 mg/kg in rats revealed no carcinogenicity findings. Proliferative changes in thyroid follicular cells was thought to be the result of induction of the hepatic enzyme responsible for metabolism of T3 and T4. There were no significant treatment effects on body weight.

4.4.4.2. Mice

Twenty-four-month oral exposure up to 30 mg/kg in mice revealed no carcinogenicity findings and no effects on body weight. Observed mortality was largely attributed to gastrointestinal dilation.

4.4.5. Special toxicity studies

A positive-controlled antigenicity study in guinea pigs demonstrated no antigenic potential from sildenafil.

Intra-arterial injection of sildenafil in rabbits revealed no clinically significant effects.

Intestinal transit time and intestinal length were increased in mice administered oral sildenafil up to 200 mg/kg over 7 or 45 days. Similarly increased intestinal transit times were seen in mice given a single dose of 200 or 400 mg/kg.

A fairly standard battery of reproductive and neonatal studies were conducted and are described in the pharmacologists' review. There were no clinically relevant findings.

4.4.6. Safety margin

The sponsor calculated (and the pharmacologists reported) safety factors based on "no adverse effect levels" in animals and a maximum recommended dose in man, as shown in Table 3 below.

Table 3. Safety factors based upon animal toxicity and human and animal pharmacokinetics.

	Sildenafil				UK-103,320			
	Mice	Rat (M)	Rat (F)	Dog	Mice	Rat (M)	Rat (F)	Dog
Dose	2	42	42	10	—			
Free C_{max}	—	0.8	19	8	—	28	8	2
Free AUC	—	0.4	40	28	—	52	35	12

4.5. Summary of significant findings

Standard and entirely adequate animal toxicology, genetic toxicology, and reproductive toxicology studies were performed. For the most part, demonstrated effects in animals were clearly related to the specific effects of sildenafil on type 5 and 6 phosphodiesterase.

5. Description of clinical data sources

5.1. Primary source data

5.1.1. Study type and design and subject enumeration

5.1.1.1. Controlled studies Table 4 below lists controlled studies of effectiveness in subjects with erectile dysfunction. Each of these studies is the subject of a brief review in Appendix A. All such studies were randomized, double-blind, placebo-controlled studies in a population with mild-to-moderate erectile dysfunction of organic, psychogenic or mixed etiologies. There were no actively-controlled studies. In most of the larger studies, the primary end point was the answer to 2 IIEF questions pertaining to sexual performance.

Table 4. Controlled clinical trials of effectiveness.

	Review	Design	Weeks	Doses mg qd	N	Etiology (%)		
						Organ	Psych	Mixed
Fixed-dose								
Study 148-102: A double-blind, randomized, placebo-controlled, parallel group, fixed-dose, multicenter study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction.	page 104	Parallel	24	25, 50, 100	532	78	9	13
Study 148-364: A double-blind, randomised, placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of fixed doses of sildenafil administered for three months to male patients with erectile dysfunction.	page 212	Parallel	12	25, 50, 100	514	43	32	25
Study 148-106: A double-blind, randomised, placebo controlled, parallel group, multicentre, fixed-dose study to assess the efficacy and safety of sildenafil administered as required to male subjects with erectile dysfunction.	page 126	Parallel	12	50, 100, 200	497	58	17	25
Study 148-101/101B: A randomised, double-blind, placebo controlled, parallel-group, fixed-dose, multicentre, long-term dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered prior to sexual activity to male patients with erectile dysfunction.	page 99	Parallel	24	5, 25, 50, 100	416	74	8	18
Study 148-353: A randomised, double-blind, placebo controlled, parallel-group, multicentre, dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered once daily for 28 days to patients with erectile dysfunction.	page 186	Parallel	4	10, 25, 50	351	—	58	42
Study 148-361: A 12-week, double-blind, placebo controlled, parallel group, multi-centre study followed by a 40 week open label extension to evaluate the efficacy and safety of UK-92,480 (sildenafil) in patients with erectile dysfunction.	page 203	Parallel	12	50, 100, 200	254	49	7	44
Titrated dose								
Study 148-103: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male patients with erectile dysfunction.	page 111	Parallel	12	25, 50, 100	329	59	15	26
Study 148-363: A double-blind, randomised, placebo-controlled, parallel group, multi-centre, flexible dose escalation study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction.	page 206	Parallel	26	25, 50, 100	315	30	32	37
Study 148-104: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male diabetic patients with erectile dysfunction.	page 118	Parallel	12	50, 100	268	96	—	4

Table 4. Controlled clinical trials of effectiveness. ***(Continued)***

	Review	Design	Weeks	Doses mg qd	N	Etiology (%)		
						Organ	Psych	Mixed
Study 148-356: A multi-centre study consisting of a 16-week open, dose-escalation phase followed by an 8-week randomised, double-blind, placebo controlled phase to assess the efficacy and safety of oral doses of UK-92,480 (sildenafil) taken as required by patients with erectile dysfunction.	page 193	Parallel	8	10-100	205	—	40	60
Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord.	page 218	Cross-over	6	50, 100	178	100	—	—
Study 148-359: A 12 week, double blind, placebo controlled, parallel group, multicentre study to evaluate a new sexual function questionnaire in the assessment of the efficacy of sildenafil (UK-92,480) in patients with erectile dysfunction.	page 199	Parallel	12	25, 50	111	40	39	8
Study 148-355: A double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of sildenafil (UK-92,480) (taken when required over a 28 day period) in patients with erectile dysfunction with no established organic cause.	page 191	Cross-over	4	25-75	44	—	100	0
Study 148-358: A two stage, double blind, placebo-controlled study to assess the efficacy and safety of oral doses of sildenafil (UK-92,480) in spinal cord injury patients with erectile dysfunction.	page 197	Parallel	4	50	27	100	—	—

This set of studies was the primary basis for the evaluation of effectiveness of sildenafil for the treatment of erectile dysfunction.

5.1.1.2. Clinical pharmacology

Studies of clinical pharmacology of sildenafil are listed in Table 5 below. Not included in this listing are those previously listed in Table 4 on page 8, but with pharmacokinetic data collected as well.

Table 5. Clinical pharmacology trials.

	Review	Design[a]	Doses mg qd	N	Purpose
Pharmacokinetics					
Study 148-001: Phase I single dose, open study of the clinical pharmacology of sildenafil in elderly and young healthy male volunteers.	page 89	OL	50	30	Effect of age
Study 148-003: Phase I open study to assess the effect of concomitant antacid administration on the absorption of sildenafil (UK-92,480) in normal, healthy male subjects.	page 94	R, OL, XO	50	12	Effect of gastric pH on absorption of sildenafil
Study 148-004: Phase I investigator-blind, placebo-controlled, evaluation of safety, toleration, and pharmacokinetics of sildenafil following escalating single oral doses in healthy male volunteers.	page 96	R, DB, PC, AD	100, 200, 300, 400, 600, 800	20	Single-dose pharmacokinetics
Study 148-203: A single blind, four way crossover study to investigate the pharmacokinetics of and assess the safety and tolerance of UK-92480 after administration of escalating intravenous doses in the fasted state.	page 131	R, SB, PC, XO	20, 40, 80 (i.v.)	8	Intravenous pharmacokinetics
Study 148-208: An open randomised, two way crossover study to investigate the pharmacokinetics of UK-92480 after oral administration and IV administration in the fasted state.	page 139	R, OL, XO	50	12	Comparison of oral and intravenous pharmacokinetics
Study 148-214: An open, parallel group study to determine the effects of impaired renal function on the pharmacokinetics, safety and toleration of sildenafil administered as a single 50 mg capsule dose.	page 142	OL	50	24	Effect of renal impairment
Study 148-215: An open, parallel group study to investigate the absorption, metabolism and excretion of a single oral and a single intravenous dose of radiolabeled [14C]-UK-92,480.	page 145	OL, II	25 (i.v.), 50 (p.o.)	6	^{14}C pharmacokinetics and metabolism
Study 148-221: An open, single dose study to compare the pharmacokinetics, safety and toleration of a single oral dose of sildenafil in patients with chronic stable hepatic cirrhosis to healthy subjects with normal hepatic function.	page 157	OL	50	12	Effect of hepatic impairment
Study 148-226: An open, randomised, single oral dose, three way crossover bioequivalence study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100mg as capsules and tablets in the fasted state.	page 163	R, OL, XO	100	37	Comparative bioavailability for different formulations
Study 148-227: An open randomised, single oral dose, two way crossover study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100 mg as commercial tablets in the fed and fasted state.	page 165	R, OL, XO	100	34	Comparison of fed and fasted pharmacokinetics

Table 5. Clinical pharmacology trials. ***(Continued)***

	Review	Design[a]	Doses mg qd	N	Purpose
Study 148-228: An open, randomised, single oral dose, four way crossover study to determine the dose proportionality of the pharmacokinetics of sildenafil in healthy male volunteers over the dose range 25mg to 200mg.	page 167	R, OL, XO	25, 50, 100, 200	33	Single-dose pharmacokinetics
Pharmacokinetic drug interaction					
Study 148-002: Phase I open study to assess the potential of cimetidine to alter the pharmacokinetics of sildenafil (UK-92,480) in normal, healthy male subjects.	page 92	R, DB, PC, II	50	22	Interaction with cimetidine
Study 148-217: A double blind, randomised, placebo controlled, three way crossover study to investigate the haemodynamic and pharmacokinetic interactions of sildenafil and alcohol in healthy male volunteers.	page 151	R, DB, PC, XO	50	12	Interaction with ethanol
Study 148-218: A double blind, randomised, placebo controlled, two-way crossover study to investigate any pharmacokinetic or pharmacodynamic interaction between orally administered UK-92,480 and tolbutamide in healthy male volunteers.	page 153	R, DB, PC, XO	50	12	Interaction with tolbutamide
Study 148-219: A double-blind, randomised, placebo-controlled, two-way crossover study to assess the potential interaction between orally administered UK-92,480 (sildenafil) and warfarin in healthy male volunteers.	page 155	R, DB, PC, XO	50	12	Interaction with warfarin
Study 148-234: An open, randomised, placebo controlled, parallel group study to investigate the effects of multiple doses of erythromycin on the pharmacokinetics of a single 100mg dose of sildenafil.	page 179	R, OL, PC, II	100	24	Interaction with erythromycin
Pharmacodynamics					
Study 148-105: A double-blind, randomised, placebo controlled, four-way crossover study to investigate the efficacy, safety and toleration of single oral dose of sildenafil (25, 50, and 100 mg) in patients with male erectile dysfunction.	page 124	R, DB, PC, XO	25, 50, 100	54	Single-dose Rigiscan
Study 148-350: A double blind, randomised, placebo controlled, two way crossover pilot study to investigate the efficacy and safety of UK-92,480 (sildenafil, 25mg tid for 7 days) in patients with impotence.	page 183	R, DB, PC, XO	75	16	Multiple-dose Rigiscan
Study 148-351: A double blind, randomised, placebo controlled, four way crossover study followed by a double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of UK-92,480 (sildenafil) in patients with erectile dysfunction with no established organic cause.	page 184	R, DB, PC, XO	10, 25, 50	12	Single-dose Rigiscan
		R, DB, PC, XO	25	12	Multiple-dose erectile function
Study 148-357: A multi-centre, double blind, randomised, placebo controlled, three way crossover study to investigate the efficacy of single oral doses of sildenafil (UK-92,480) in diabetic patients with penile erectile dysfunction.	page 195	R, DB, PC, XO	25, 50	21	Single-dose Rigiscan in diabetics
		R, DB, PC, II	50	21	Multiple-dose erectile function in diabetics
Study 148-358: A two stage, double blind, placebo-controlled study to assess the efficacy and safety of oral doses of sildenafil (UK-92,480) in spinal cord injury patients with erectile dysfunction.	page 197	R, DB, PC, XO	50	27	Single-dose Rigiscan
		R, DB, PC, II	50	27	Multiple-dose erectile function in diabetics
Study 148-360: A double-blind, randomised, placebo controlled, two-way crossover study to investigate the onset of action of single oral doses of UK-92,480 (sildenafil) 50mg in patients with penile erectile dysfunction without an established organic cause.	page 201	R, DB, PC, XO	50	17	Single-dose Rigiscan in spinal cord injury
Study 148-369: A double blind, randomised, placebo controlled, sequential design, two way crossover study to investigate the duration of action of a single oral dose of sildenafil (100 mg) on penile erectile activity during visual sexual stimulation in patients with male erectile dysfunction without an established organic cause.	page 222	R, DB, PC, XO	100	16	Single-dose Rigiscan in psychogenic erectile dysfunction
Study 148-204: An open study in normal volunteers to investigate the effects of an escalating brachial artery infusion of UK-92,480 on forearm blood flow and forearm venous compliance.	page 133	OL, BL	0.003-1 (i.a.)	12	Forearm blood flow
Study 148-301: An open single intravenous dose study of the haemodynamic effects of UK-92,480 (sildenafil) in patients with stable ischaemic heart disease.	page 181	OL	40 (i.v.)	8	Invasive hemodynamics
Pharmacodynamic drug interaction					
Study 148-209: A double blind, randomised, placebo controlled, two-way crossover study to examine the effects of 25mg tid UK-92,480, administered as capsules, on the haemodynamic responses to glyceryl trinitrate in normal volunteers.	page 141	R, DB, PC, XO	75	12	Blood pressure response to nitroglycerin

Table 5. Clinical pharmacology trials. ***(Continued)***

	Review	Design[a]	Doses mg qd	N	Purpose
Study 148-216: An open study to investigate the effects of a single dose of UK-92,480 (50mg) on bleeding time, followed by a double-blind, placebo-controlled, two-way crossover study to investigate the effects of a single dose of UK-92,480 (50mg) on aspirin-induced prolongation of bleeding time in healthy male volunteers.	page 150	R, DB, PC, XO	50	18	Bleeding time
Study 148-222: Single blind, placebo controlled, parallel group study to investigate the effects of a single oral dose of sildenafil (UK-92,480) (100mg) and isosorbide dinitrate (20mg) on aspirin-induced prolongation of bleeding time in healthy male volunteers.	page 159	R, RB, PC, ‖	100	45	Bleeding time
Study 148-225: A double-blind, placebo controlled, two way crossover study to investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in subjects with essential hypertension being treated with amlodipine.	page 162	R, DB, PC, XO	100	16	Blood pressure response with amlodipine
Study 148-230: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking isosorbide mononitrate oral therapy.	page 173	R, DB, PC, XO	50	16	Blood pressure response with isosorbide mononitrate
Study 148-231: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking sublingual glyceryl trinitrate (GTN) therapy.	page 175	R, DB, PC, XO	50	16	Blood pressure response with glyceryl trinitrate
Special safety and other					
Study 148-206: A single blind, two way crossover, placebo controlled pilot study to investigate the effects of UK-92,480 (sildenafil) on platelet function in normal male volunteers.	page 134	R, SB, PC, XO	50	8	Platelet function
Study 148-207: A double blind, placebo controlled, single dose study followed by a double blind, placebo controlled 10-day multiple dose study to investigate the pharmacokinetics, platelet effects, safety and toleration of UK-92,480 (sildenafil) in healthy male volunteers.	page 135	R, DB, PC, ‖	25, 50, 75	38	Platelet function
Study 148-223: A double-blind, randomised, placebo controlled, four period crossover study to assess the effect of orally administered sildenafil (50, 100 and 200mg) on visual function in healthy male volunteers.	page 160	R, DB, PC, XO	50, 100, 200	16	Vision
Study 148-229: A double-blind, randomised, single oral dose, four period, two-way crossover pilot study to investigate the acute effects of sildenafil on sperm motility.	page 170	R, DB, PC, XO	100	17	Sperm motility
Study 148-232: A randomised, double-blind, placebo-controlled, crossover pilot study to investigate the effects of a single oral tablet dose of sildenafil (200mg) on visual function (electroretinogram, photostress, visual field and colour discrimination tests) in healthy male volunteers and patients with diabetic retinopathy.	page 177	R, DB, PC, XO	200	16[b]	Vision
Study 148-401: Statistical report a psychometric validation of the international index of erectile function (IIEF) in male patients with erectile dysfunction and age-matched controls.	page 223	ED vs normal control	None	58	IIEF validation
Study 148-451: A study to generate sexual function and quality of life data in male subjects who do not have a diagnosis of erectile dysfunction.	page 224	Normal control	None	109	IIEF validation

a. R=randomized; DB=double-blind; OL=open-label; PC=placebo-controlled; AC=active-control; AD=ascending dose; ‖=parallel; XO=cross-over.

b. Includes 8 subjects with diabetic retinopathy for whom no data were reported.

5.1.1.3. Open-label extensions

Other studies contributing to the safety assessment, generally long-term extensions to other studies listed here, are listed in Table 6 below. A few completed studies are subjects of individual study reports. Studies shown without a review were listed as being in progress as of the cut-off date for the NDA. All such contributed to the open-label safety experience, but studies in progress did not have complete reporting of adverse events.

Table 6. Long-term, open-label studies.

	Review	Extension to studies
Study 148-101C: An open, non-comparative study to assess the long-term safety of sildenafil in patients with erectile dysfunction.	page 102	148-101/101B
Study 148-354A: An open, non-comparative study to assess the efficacy and safety of UK-92,480 (sildenafil) taken over a 52-week period by patients with erectile dysfunction.	page 189	148-350, 148-351, 148-353, 148-355
Study 148-102C: An open, non comparative study to assess the long-term safety of sildenafil in patients with erectile dysfunction	—	148-102
Study 148-103C: An open, non comparative study to assess the Long-Term safety of sildenafil in patients with erectile dysfunction	—	148-103
Study 148-104C: An open, non comparative study to assess the long-term safety of sildenafil in diabetic patients with erectile dysfunction	—	148-104
Study 148-354B: An open non-comparative study to assess the efficacy and safety of UK-92,480 taken over a 52 week period by patients with erectile dysfunction	—	148-356
Study 148-354C: An open non-comparative study to assess the efficacy and safety of UK-92,480 taken over a 52 week period by patients with erectile dysfunction	—	148-355, 148-357, 148-358, 148-359, 148-360, 166-301
Study 148-366: An open, non comparative study to assess the long-term safety of sildenafil in patients with erectile dysfunction	—	148-363
Study 148-365: An open non-comparative study to assess the long term safety and efficacy of sildenafil (UK-92,480) in patients with erectile dysfunction	—	148-354A, 148-354B
Study 148-361OCS: A 12 week double blind placebo controlled parallel group multicentre study followed by a 40 week open label extension to evaluate the efficacy and safety of UK-92,480 in patients with erectile dysfunction	—	148-361

5.1.1.4. Studies not reviewed in detail

Some studies were not subjected to detailed clinical review. These are listed in Table 7 below. They contribute to the safety database, but they are not otherwise considered in this review document.

Table 7. Studies not reviewed in detail.

	Comment
Study 148-201: A single blind dose escalating single oral dose study to assess the safety, toleration and pharmacokinetics of UK-92,480	Single-dose pharmacokinetics covering 1.25 to 90 mg
Study 148-201A: An extension to a single blind dose escalating single oral dose study to assess the safety, toleration and pharmacokinetics of UK-92,480	Single-dose pharmacokinetics covering 100 to 200 mg
Study 148-202: An open randomized three way crossover study to investigate the pharmacokineticsof UK-92,480 after oral administration as a solution in the fasted state and as a capsule in the fed and fasted state.	Not relevant
Study 148-205: An open study in normal volunteers to compare the effects of escalating intravenous doses of UK-92,480 and GTN on human dorsal hand vein tone	Failed study
Study 148-210: An open randomized pilot study in normal subjects to assess the pharmacokinetics of UK-92,480 after oral administration of 50 mg as a solution and as three sustained release preparations	Not relevant
Study 148-211: A double blind double dummy randomized placebo controlled 8 day multiple dose study to investigate the pharmacokinetics, pharmacodynamics, safety and toleration of orally administered UK-92,480 in healthy male volunteers	Not relevant
Study 148-213: An open randomized three way crossover study to determine the pharmacokinetics of UK-92,480 in healthy male volunteers following oral administration of 50 mg as capsules and as tablets in the fasted state	Not relevant
Study 148-220: An open randomized single dose three way crossover bioequivalence study to determine the pharmacokinetics of UK-92,480 in healthy male volunteers following oral administration of 50 mg as capsules and as tablets in the fasted state	Not relevant
Study 166-301: A double-blind, randomized, placebo-controlled, three-way crossover study to investigate and compare efficacy of a single oral solution dose of UK-114,542 with that of sildenafil (UK-92,480) in patients with no established organic cause	N=10, comparison with a similar compound
Study JP-95-501: A phase I single dose study of UK-92,480 capsule	Japanese pharmacokinetics
Study JP-95-502: A phase I food interaction study of UK-92,480 capsule	Japanese food-effect
Study JP-95-503: A phase I day multiple dose study of UK-92,480 capsule	Japanese multiple-dose pharmacokinetics
Study JP-96-601: An early phase II study of UK-92,480 capsule in patients with male erectile dysfunction	Japanese pharmacokinetics

5.1.2. Enumeration

Table 8 below is a summary of the numbers of subjects exposed in the sponsor's development program.

Table 8. Subjects exposed in clinical studies.

	Pcbo	Sildenafil		
		Only	Pcbo ⇒	Total
Phase I				
IV	28	—	—	55
PO	215	—	—	533
Total	243	—	—	576
Phase II/III				
Single-dose		98	—	98
PRN		2600	769	3369
Multiple-daily		305	—	305
Total	1832	3003	769	3772
Japanese	16	—	—	178
Total	2091	—	—	4526

5.1.3. Demographics

Table 9 below shows the distribution of subjects' age in placebo-controlled and open-label studies of sildenafil. All subjects were males and exceedingly few subjects were non-Caucasian.

Table 9. Subjects by age in placebo-controlled and open-label studies.

	Age (years)								Tot
	18-28	28-38	38-48	48-58	58-68	68-78	78-88	88+	
Placebo-controlled	10	124	351	930	1373	993	152	2	3935
Open-label	2	33	154	545	790	595	79	1	2199

Table 10 below shows the distribution of etiologies of erectile dysfunction in placebo-controlled and open-label studies.

Table 10. Etiology of erectile dysfunction in placebo-controlled and open-label studies.

	Etiology					Total
	Organic	Psychogenic	Mixed	None	Other	
Placebo-controlled	2069	720	1016	117	13	3935
Open-label	1037	505	616	33	8	2199

Baseline diseases in placebo-controlled and open-label studies are described in Table 11 below.

Table 11. Baseline disease incidence (%) in placebo-controlled and open-label studies.

	PC N=3935	OL N=2199		PC N=3935	OL N=2199
Hypertension	25	27	Depression	5.1	5.4
Diuretics	4.4	2.5	Antidepressants	3.5	1.9
Other antihypertensives	24	14	Other psychiatric illness	2.9	3.2
Smoking	24	14	Spinal cord injury	4.5	0
Diabetes mellitus	18	19	Other neurological disease	1.7	1.4
Hyperlipidemia	14	15	Peripheral vascular disease	2.3	2.2
Cardiovascular disease	14	15	Peyronie's disease	1.9	1.5
Transurethral prostatectomy	5.5	4.2	Cerebrovascular disease	1.7	1.5
Radical prostatectomy	4.4	3.9	Chronic obstructive pulm disease	1.6	1.8

5.1.4. Extent of exposure

Characterizing exposure to study drug is complicated by two factors. The bulk of the experience was with p.r.n. dosing, so the period of exposure is a poor index, and the actual doses received were not captured in the sponsor's integrated clinical database.

5.1.4.1. Placebo-controlled experience

Study reports for only 2 fixed-dose trials were accompanied by full datasets permitting an assessment of drug exposure, as shown in Table 12 below.

Table 12. Study drug exposure (doses) in studies 148-102 and 148-361.

Study	Wks	Placebo		Sildenafil								
				25 mg		50 mg		100 mg		Any		
		N	Doses	N	Doses	N	Doses	N	Doses	N	Doses	Rate[a]
148-102	24	216	14004	102	7023	107	7795	107	7055	316	21873	2.9
148-364	12	127	3705	128	4313	132	4192	127	4062	387	12567	2.7

a. Per subject per week

Planned exposure in weeks for all fixed-dose studies in shown in Table 13 below. Because of subject withdrawals, actual exposure was 3.8% less (total of about 520 subject-years) in the active treatment groups.

Table 13. Planned exposure (weeks) in placebo-controlled fixed-dose studies.

Study	Weeks	Plcbo N	Sildenafil						
			5 mg N	10 mg N	25 mg N	50 mg N	100 mg N	200 mg N	Any N
148-102	24	216	—	—	102	107	107	—	316
148-364	12	127	—	—	128	132	127	—	387
148-106	12	122	—	—	—	127	124	124	375
148-101/101B	24	83	86	—	82	83	82	—	333
148-353	4	95	—	90	85	81	—	—	256
148-361	12	59	—	—	—	62	66	67	195
Subjects		702	86	90	397	592	587	191	1862
Subject-weeks		11252	2064	360	6292	8736	8340	2292	28084

Exposure to sildenafil in placebo-controlled, titrated-dose studies (148-363, 148-103, 148-104, 148-367, 148-359, 148-355, and 5 smaller studies) totalled 9090 subject-weeks (175 subject-years).

5.1.4.2. Open-label experience

Open-label experience in Studies 148-354A, 148-101C, 148-354B, 148-102C, 148-361O, 148-365, 148-103C, 148-366, 148-104C, and 148-354C contributed a total of almost 49000 subject-weeks (942 subject-years) of exposure to sildenafil. Although dose information does not appear in the sponsor's integrated database, by trial design little of this experience lies with doses other than 50 and 100 mg.

The sponsor indicates that 559 subjects received treatment over 1 year.

5.1.4.3. Safety updates

By agreement with the Division and in consideration of the compressed time frame for review, the sponsor's safety update was restricted to deaths and serious adverse events.

5.2. Secondary source data

5.2.1. Other studies

None applicable.

5.2.2. Post-marketing experience

Sildenafil is not approved for marketing in any country.

5.2.3. Literature

A search of the on-line catalog at NLM revealed only two published descriptions of clinical trials of sildenafil. Both publications appear to refer to the same small, pilot study of sildenafil in subjects with erectile dysfunction of psychogenic etiology. Neither publication was reviewed in detail.

5.3. Adequacy of clinical experience

Almost 1000 subjects have participated in fixed-dose, placebo-controlled studies for 6 months, and another 1500 have been in such studies for 1 to 3 months. Placebo-controlled titration studies of 1 to 6 months involved another 1500 subjects. Open-label studies contribute around 1000 subject-years of exposure to sildenafil.

Whether this level of safety assessment is adequate for a drug intended to provide benefit in some aspect of quality of life is a matter of judgement, but the degree of sampling in this development program is comparable to the typical database for a new antihypertensive agent, for which there is at least the expectation of an effect on morbidity and mortality.

5.4. Data quality and completeness

Full study reports have been provided for all pertinent clinical studies. Complete machine-readable data were provided for well-controlled studies.

DSI audit of a sampling of centers in major studies uncovered no problems of a material nature.

Outside of the DSI audit, there was no attempt made as part of this review to reconcile datasets with case report forms.

6. Clinical pharmacology and biopharmaceutics

6.1. Bioavailability/bioequivalence

6.1.1. Absolute bioavailability

The absolute bioavailability of a single 50-mg sildenafil dose, relative to an intravenous dose of 50 mg infused at a rate of 1 mg/min, was estimated to be 41%. These results are in good agreement with the results of the ^{14}C study[1] in which the absolute bioavailability was estimated to be 38%.

Study 148-215 showed that the absorption of sildenafil was approximately 90% calculated from the ratio of unchanged drug in the excreta (oral/intravenous). Sildenafil accounted for 60% of the total circulating radioactivity after intravenous administration and 32% after oral administration.

6.1.2. Food effects

The results of study 148-227[2] show that the co-administration of a high-fat breakfast with a single 100-mg commercial tablet decreased the rate of absorption of sildenafil. C_{max} decreased from 514 ng/mL in the fasted state to 364 ng/mL in the fed state. Sildenafil AUC in the fasted state was 1651 ng.h/mL compared to 1489 ng.h/mL in the fed state. The time to peak concentration was prolonged by 1 hour (from 1 to 2 hours) in the fed state. The same trends were observed for the metabolite, where C_{max} decreased from 215 to 137 ng/mL and AUC decreased from 729 ng.h/mL in the fasted state to 571 ng.h/mL in the fed state. This decrease in the rate of absorption is not expected to have any clinical consequences. The results of the above study were confirmed by the population pharmacokinetic study[3] where food was found to be a significant covariate on the absorption rate constant.

6.1.3. Bioequivalence

Study 148-226[4] showed that the 25-mg research capsule (given as 4x25 mg capsules), the 100-mg research tablet and the 100-mg commercial tablet formulations are bioequivalent to each other. Both sildenafil and its metabolite meet the 90% confidence intervals of 80 to 125%. Since the metabolite UK-103,320 has about 50% of the specific activity of sildenafil and its plasma levels are about 40% of sildenafil's, UK-103,320 contributes about 15% of the drug effect and so its bioequivalence is not considered important.

6.2. Pharmacokinetics

6.2.1. Single-dose pharmacokinetics

After single oral doses of sildenafil, absorption of sildenafil is rapid with mean T_{max} around 0.8 to 1 hour. Sildenafil plasma concentrations appear to decline in a bi-exponential manner with an apparent oral clearance of 41 L/h. Sildenafil's apparent steady-state volume of distribution was estimated to be 105 L. The elimination half-life was estimated to be around 3 to 4 hours.

For metabolite UK-103,320, the maximum observed concentrations occurred within 1 hour of dosing. The elimination half-life for this metabolite was of the same order as the parent drug—between 3 and 4 hours. The plasma concentrations of the active metabolite were approximately 40% of those seen for sildenafil after oral dosing and 15% after intravenous dosing.

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1. *Study 148-215: An open, parallel group study to investigate the absorption, metabolism and excretion of a single oral and a single intravenous dose of radiolabeled [14C]-UK-92,480.* on page 145.
2. *Study 148-227: An open randomised, single oral dose, two way crossover study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100 mg as commercial tablets in the fed and fasted state.* on page 165.
3. *Population pharmacokinetic and pharmacodynamic analysis of sildenafil phase III data.* on page 75.
4. *Study 148-226: An open, randomised, single oral dose, three way crossover bioequivalence study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100mg as capsules and tablets in the fasted state.* on page 163.

6.2.2. Multiple-dose pharmacokinetics

Three-times daily administration of sildenafil for eight days produced slight accumulation at all the studied doses. The accumulation ratios between day 9 and single-dose administration, based on AUC_{0-8h}, for the 25-, 50- and 75-mg doses were 1.26, 1.59, and 1.32, respectively. The corresponding accumulation ratios, based on C_{max}, were 1.07, 1.55, and 1.09. The same degree of accumulation was also observed for the metabolite UK-103,320[5]. However, since the maximum recommended dosing frequency is once daily, no clinically significant accumulation is expected.

6.2.3. ADME

Five primary pathways have been identified for sildenafil namely demethylation at either the N methyl piperazine and/or N-methyl pyrazole moieties, oxidation of the piperazine ring, loss of a two-carbon piperazine ring and aliphatic hydroxylation. Secondary pathways include multiple combinations of the primary pathways in addition to further oxidation and demethylation of the piperazine ring. The metabolic profile of sildenafil is summarized in Figure 2 below.

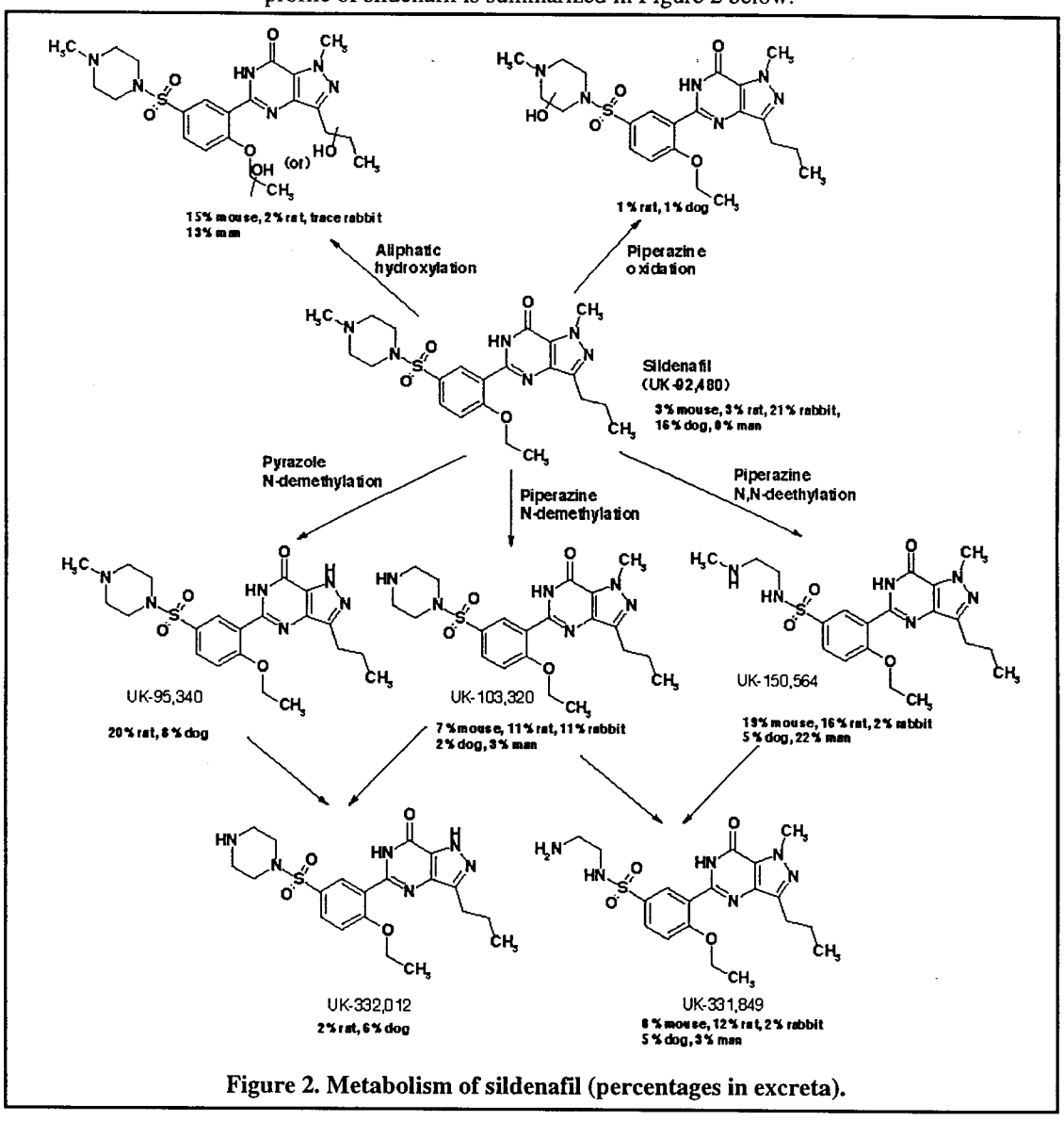

Figure 2. Metabolism of sildenafil (percentages in excreta).

[5] *Study 148-207: A double blind, placebo controlled, single dose study followed by a double blind, placebo controlled 10-day multiple dose study to investigate the pharmacokinetics, platelet effects, safety and toleration of UK-92,480 (sildenafil) in healthy male volunteers.* on page 135.

The metabolite profiles were qualitatively similar for the oral and intravenous route. The major component found in urine up to 24 hours was the aliphatic hydroxylated metabolite. The major component in fecal recoveries up to 72 hours post-dosing was UK-150,564. A further 16 metabolites were identified, individually accounting for less than 5% of the dose. There was no unchanged sildenafil detected in either the urine or feces.

In vitro studies have identified that the metabolism of sildenafil occurs in human hepatic microsomes and is mediated by two P450 isoforms, CYP2C9 and CYP3A4.

The major circulating metabolites after oral dosing were identified as UK-103,320, which was present at concentrations around 40% of the parent drug and UK-150,564, which was present at concentrations around 25% of those of the parent drug.

The majority of the radioactivity was excreted in the feces—76% of the intravenous dose and 79% of the oral dose. Less than 4% of the administered dose was excreted in the urine as sildenafil or UK-103,320[6].

In vitro studies have demonstrated that UK-103,320 has around 50% of the potency of sildenafil as a phosphodiesterase inhibitor. The major excretory metabolite UK-150,564 has 10% of the potency of sildenafil.

6.2.4. Plasma level-dose relationship

Study 148-228[7] showed that, in the dosing range between 10 and 200 mg, the pharmacokinetic parameters of sildenafil slightly deviate from proportionality. However, at doses above 200 mg, this non-proportionality becomes pronounced. At a dose of 800 mg, the AUC and C_{max} for sildenafil were 25686 ng.h/mL and 5834 ng/mL, respectively, while at a dose of 100 mg the values were 1691 ng.h/mL and 411 ng/mL, respectively. For an 8-fold increase in dose, there was a 15- and 14-fold increase in AUC and C_{max}, respectively. The same trend of results were observed for UK-103,320[8]. This pronounced nonlinearity is probably a result of saturation of the metabolic pathways of sildenafil and metabolite.

Study 148-203[9] showed that after intravenous administration, nonlinearity is evidenced at lower doses (in the range between 20 and 80 mg). The power functions indicated that non-proportionality was not extensive, with a 2-fold dose increase giving an approximately 2.5-fold increase in C_{max} and a 2.4-fold increase in AUC.

6.2.5. Concentrations in semen

The mean concentrations of sildenafil in the ejaculate, 1.5 and 4.5 hours post-dose were 18 and 17%, respectively, of those in plasma at the same time points. The concentrations of the metabolite at the same time points were 5 and 15% of those in the plasma. There were highly statistically significant relationships between the concentrations of sildenafil or UK-103,320 in semen and the total and free plasma concentrations[10].

6.2.6. Protein binding

The protein binding of sildenafil and metabolite UK-103,320 is high (96% bound) and is independent of the concentrations over the clinically relevant concentration range.

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6. *Study 148-215: An open, parallel group study to investigate the absorption, metabolism and excretion of a single oral and a single intravenous dose of radiolabeled [14C]-UK-92,480.* on page 145.
7. *Study 148-228: An open, randomised, single oral dose, four way crossover study to determine the dose proportionality of the pharmacokinetics of sildenafil in healthy male volunteers over the dose range 25mg to 200mg.* on page 167
8. *Study 148-004: Phase I investigator-blind, placebo-controlled, evaluation of safety, toleration, and pharmacokinetics of sildenafil following escalating single oral doses in healthy male volunteers.* on page 96.
9. *Study 148-203: A single blind, four way crossover study to investigate the pharmacokinetics of and assess the safety and tolerance of UK-92480 after administration of escalating intravenous doses in the fasted state.* on page 131.
10. *Study 148-229: A double-blind, randomised, single oral dose, four period, two-way crossover pilot study to investigate the acute effects of sildenafil on sperm motility.* on page 170.

6.3. Special populations

6.3.1. Renal impairment

The pharmacokinetics of sildenafil and its active metabolite were significantly altered in subjects with severe renal impairment (CLcr <30 mL/min). Both the systemic exposure to sildenafil and metabolite and peak plasma concentrations were almost twice as high in this subject population compared to their healthy counterparts. The AUC for the parent drug was 1519 ng.h/mL, compared to 756 ng.h/mL, and C_{max} was 464 ng/mL, compared to 246 ng/mL for healthy volunteers. These findings were accompanied by an increased inter-subject variability in the severely impaired subjects. There were no significant differences across the various groups in protein binding (free fraction ranged from 2 to 2.7%). Moreover, there was a good correlation between C_{max}, AUC, or apparent oral clearance and the degree of renal impairment. The increased exposure is attributed to a reduction in apparent oral clearance which is directly related to the effects of renal impairment or to the effects of renal impairment on hepatic function or hepatic blood flow[11]. The effects of hemodialysis on the pharmacokinetics of sildenafil and its major metabolite was not investigated.

Based on the above results, consideration should be given to starting patients with severe renal impairment at a dose of 25 mg and titrating upwards as indicated.

6.3.2. Hepatic impairment

Study 148-221[12] showed that chronic stable hepatic cirrhosis alters the pharmacokinetics of sildenafil. The apparent clearance for the cirrhotic subjects was 46% lower leading to an 85% increase in exposure (AUC increased from 664 to 1226 ng.h/mL and C_{max} increased from 155 to 228 ng/mL after the administration of a single 50-mg dose). These results were confirmed by the population pharmacokinetic analysis that the sponsor undertook. A statistically significant relationship between SGOT (AST) levels and the sildenafil and UK-103,320 levels was found. There were 6% and 9% decreases in CL/F for every 10-unit increase of AST, for sildenafil and UK-103,320, respectively. Based on the above results, consideration should be given to starting patients with impaired liver function at a dose of 25 mg and titrating upwards as indicated.

6.3.3. Age

The results of study 148-001[13] showed that subjects of age greater than 65 years had a significantly reduced apparent clearance of sildenafil after a single 50-mg dose. CL/F was reduced about 50%, leading to an increase in AUC, compared to the young, from 586 to 1077 ng.h/mL and in C_{max} from 178 to 302 ng/mL. The differences in clearances between these two populations were attributed, by the sponsor, to differences in protein binding. The protein binding in the elderly was 96.6% compared to 95.7% in the young. Similar trends in the results were also observed for the metabolite where the plasma concentrations were doubled in the elderly compared to the young.

The population analysis confirmed the findings of study 148-001, suggesting an inverse relationship between age and apparent clearance of sildenafil. There was a 4% decrease in CL/F for each decade increase in age. Based on the above results, consideration should be given to starting patients of age greater than 65 years at a dose of 25 mg and titrating upwards as indicated.

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11. *Study 148-214: An open, parallel group study to determine the effects of impaired renal function on the pharmacokinetics, safety and toleration of sildenafil administered as a single 50 mg capsule dose.* on page 142.
12. *Study 148-221: An open, single dose study to compare the pharmacokinetics, safety and toleration of a single oral dose of sildenafil in patients with chronic stable hepatic cirrhosis to healthy subjects with normal hepatic function.* on page 157.
13. *Study 148-001: Phase I single dose, open study of the clinical pharmacology of sildenafil in elderly and young healthy male volunteers.* on page 89.

6.3.4. Diabetes

Diabetes did not affect the pharmacokinetics of either sildenafil or metabolite UK-103,320[14].

6.3.5. Erectile dysfunction

Subjects with erectile dysfunction achieved the same sildenafil plasma levels as their healthy counterparts.

6.4. Drug interactions

6.4.1. Tolbutamide

The co-administration of a single 50-mg dose of sildenafil did not have any effect on the pharmacokinetics of a single 250-mg dose of tolbutamide[15].

6.4.2. Warfarin

The co-administration of multiple 50-mg doses of sildenafil did not have any effect on either the bleeding time or prothrombin time associated with a single 40-mg dose of warfarin[16].

6.4.3. Ethanol

The co-administration of a single 50-mg dose of sildenafil did not have any effect on the pharmacokinetics or hemodynamic effects of a single 0.5 g/kg dose of ethanol[17].

6.4.4. Calcium channel blockers

The co-administration of a single 100-mg dose of sildenafil to mild hypertensive subjects stabilized on amlodipine 5 or 10 mg did not have any effects on either the pharmacokinetics or pharmacodynamic effects of amlodipine[18].

The population pharmacokinetic analysis showed that co-administration of calcium channel blockers did not have any effects on the pharmacokinetics of either sildenafil or its metabolite.

6.4.5. Cimetidine

Study 148-002[19] investigated the effects of the co-administration of multiple 800-mg doses of cimetidine with a single 50-mg dose of sildenafil in healthy male volunteers. The results showed that cimetidine increased sildenafil's AUC by 56% and C_{max} by 54%. The AUC of UK-103,320 was increased by 30% without any increase in C_{max}. The magnitude of this pharmacokinetic interaction is not expected to have any clinical consequences.

6.4.6. Maalox

The co-administration of maalox with sildenafil does not affect the pharmacokinetics of either sildenafil or UK-103,320[20].

6.4.7. Erythromycin

The co-administration of multiple doses of erythromycin with a single 100-mg dose of sildenafil increased sildenafil's AUC 2.6-fold and C_{max} 2.1-fold. However, the same effect was not shown on metabolite UK-103,320, where the ratio of geometric AUC means was 1.2 and the ratio of geometric C_{max} means was 0.6. The sponsor attributed the increased sildenafil plasma levels to the inhibition of gastrointestinal CYP3A4 by erythromycin, thereby affecting the pre-systemic metabolism of sildenafil. The magnitude of increase in plasma levels suggests that one should consider starting

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14. *Study 148-232: A randomised, double-blind, placebo-controlled, crossover pilot study to investigate the effects of a single oral tablet dose of sildenafil (200mg) on visual function (electroretinogram, photostress, visual field and colour discrimination tests) in healthy male volunteers and patients with diabetic retinopathy.* on page 177.
15. *Study 148-218: A double blind, randomised, placebo controlled, two-way crossover study to investigate any pharmacokinetic or pharmacodynamic interaction between orally administered UK-92,480 and tolbutamide in healthy male volunteers.* on page 153.
16. *Study 148-219: A double-blind, randomised, placebo-controlled, two-way crossover study to assess the potential interaction between orally administered UK-92,480 (sildenafil) and warfarin in healthy male volunteers.* on page 155.
17. *Study 148-217: A double blind, randomised, placebo controlled, three way crossover study to investigate the haemodynamic and pharmacokinetic interactions of sildenafil and alcohol in healthy male volunteers.* on page 151.
18. *Study 148-225: A double-blind, placebo controlled, two way crossover study to investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in subjects with essential hypertension being treated with amlodipine.* on page 162.
19. *Study 148-002: Phase I open study to assess the potential of cimetidine to alter the pharmacokinetics of sildenafil (UK-92,480) in normal, healthy male subjects.* on page 92.
20. *Study 148-003: Phase I open study to assess the effect of concomitant antacid administration on the absorption of sildenafil (UK-92,480) in normal, healthy male subjects.* on page 94.

patients who are on known inhibitors of CYP3A4 on sildenafil 25 mg and titrating upwards as indicated[21].

6.4.8. CYP3A4 inducers

The population pharmacokinetic analysis showed that co-administration of CYP3A4 inducers, such as rifampin, did not have any effects on the pharmacokinetics of either sildenafil or its metabolite. However, this analysis only included 31 subjects who were on these concomitant drugs and, therefore, these observations should be considered inconclusive. It is expected that since CYP3A4 is a major route of metabolism, co-administration of CYP3A4 inducers will lead to decreased sildenafil levels.

6.4.9. Diuretics

The population pharmacokinetic analysis showed that loop and potassium-sparing diuretics decreased the apparent clearance of the metabolite UK-103,320 by 31%. This effect on the metabolite clearance is not expected to be of clinical significance. Moreover, this analysis showed that thiazide and related diuretics did not have any effects on the pharmacokinetics of sildenafil or its metabolite. Because there were only 36 subjects on these concomitant medications, the results of these analyses should be considered inconclusive.

6.4.10. β-blockers

The population pharmacokinetic analysis revealed that nonspecific β-blockers decreased the apparent clearance of UK-103,320 by 51%. This decrease in clearance of the metabolite is not expected to be of clinical consequence. Cardio-selective β-blockers were found to have no effects.

6.4.11. CYP2C9 inhibitors

The population pharmacokinetic analysis showed that co-administration of CYP2C9 inhibitors, such as tolbutamide or warfarin, did not have any effects on the pharmacokinetics of either sildenafil or its metabolite.

6.4.12. CYP2D6 inhibitors

The population pharmacokinetic analysis showed that co-administration of CYP2D6 inhibitors did not have any effects on the pharmacokinetics of either sildenafil or its metabolite.

6.4.13. ACE inhibitors and angiotensin II antagonists

The population pharmacokinetic analysis showed that co-administration of either ACE inhibitors or angiotensin II antagonists did not have any effects on the pharmacokinetics of either sildenafil or its metabolite.

6.4.14. Inhibition of CYP by sildenafil and UK-103,320

In vitro metabolic inhibition studies showed that, at the clinically relevant concentrations, neither sildenafil nor UK-103,320 had any inhibitory effects on any of the relevant CYP isozymes tested.

6.5. Population pharmacokinetic analysis

For sildenafil, the population-typical values (mean±SE) were 59±1.4 L/h for apparent clearance, 310±6.9 L for apparent volume of distribution, and 2.6±0.2 h^{-1} for K_a. The inter-individual variabilities (mean±SE of the variance) were 29±20% for CL/F, 20±50% for V/F, and 210±25% for K_a. The level of residual variability was 48±12%.

For UK-103,320, the population-typical values were 109±3.7 L/h for apparent clearance, 736±35 L for apparent volume of distribution, and 2.6±0.2 h^{-1} for the formation rate constant. The inter-individual variabilities were 49±21% for apparent clearance, 38±29% for apparent volume of distribution, and 292±21% for the formation rate constant. The level of residual variability was 46±12%.

6.6. Pharmacokinetic/pharmacodynamic relationships

Asymptotic E_{max} models with baseline and placebo components were used to describe the efficacy data. It was found that neither drug AUC nor metabolite AUC performed

[21] *Study 148-234: An open, randomised, placebo controlled, parallel group study to investigate the effects of multiple doses of erythromycin on the pharmacokinetics of a single 100mg dose of sildenafil.* on page 179.

better as a predictor of outcome than did dose. An additive model (i.e., an absolute change from baseline) was more appropriate than a relative change.

There was no obvious correlation between plasma concentrations of sildenafil and its metabolite and time to onset of erections or duration of rigidity. The mean duration of rigidity ≥60% at the base of the penis was 22 minutes for both 0- to 50- and 50- to 100-ng/mL ranges. At concentrations above 100 ng/mL, all responses exceeded 30 minutes.

The incidence of adverse events was much larger with the 200-mg dose than with lower doses. With the 200-mg dose, AUC values in excess of 2600 ng.h/mL and C_{max} values in excess of 500 ng/mL were associated with a 40% incidence of abnormal vision episodes, 15% incidence of gastrointestinal events, and 25% incidence of vascular events.

6.7. Formulations

The 25, 50 and 100 mg commercial tablet formulations are compositionally proportional, as shown in Table 14 below.

Table 14. Composition (mg) of sildenafil tablets.

	25 mg	50 mg	100 mg
Sildenafil citrate	35.112	70.225	140.450
Microcrystalline cellulose			
Dibasic calcium phosphate, anhydrous			
Croscarmelose sodium			
Magnesium stearate			
Blue			
Purified water			
Clear			

6.8. Dissolution

The sponsor undertook a series of dissolution studies in order to select the best dissolution conditions for sildenafil. Figure 3 below shows the results of the dissolution of 100-mg tablets under various rotation speeds. The sponsor found that with the USP apparatus II the phenomenon of coning was occurring. Tablets coming to rest at the bottom dead center exhibited most coning and therefore had the lowest release. Moreover, the sponsor found that complete release of sildenafil from the tablet matrix was not possible at a paddle speed of 50 rpm even with extended dissolution times. For the above reasons the sponsor chose a speed of 100 rpm for the dissolution apparatus. Figure 4 below shows the dissolution of sildenafil 25-mg tablets in the various media tested in 900 mL at a basket speed of 100 rpm.

It was observed that in water, there was a small reduction in release after storage in high humidity environments. This phenomenon was eliminated by switching the dissolution medium to 0.9% saline. Moreover, it was the opinion of the sponsor that water was a hyper-discriminating medium and thus they opted to use 0.01 M hydrochloric acid as the dissolution medium. The proposed specification was Q= in 30 minutes.

Figure 5 below shows the dissolution profiles, obtained with the proposed dissolution method, for the 25-, 50-, and 100-mg tablets, with and without the cosmetic coat. The results show that dissolution of sildenafil tablets, with and without the cosmetic coat, are similar and very rapid. Based on these results, the following dissolution method is

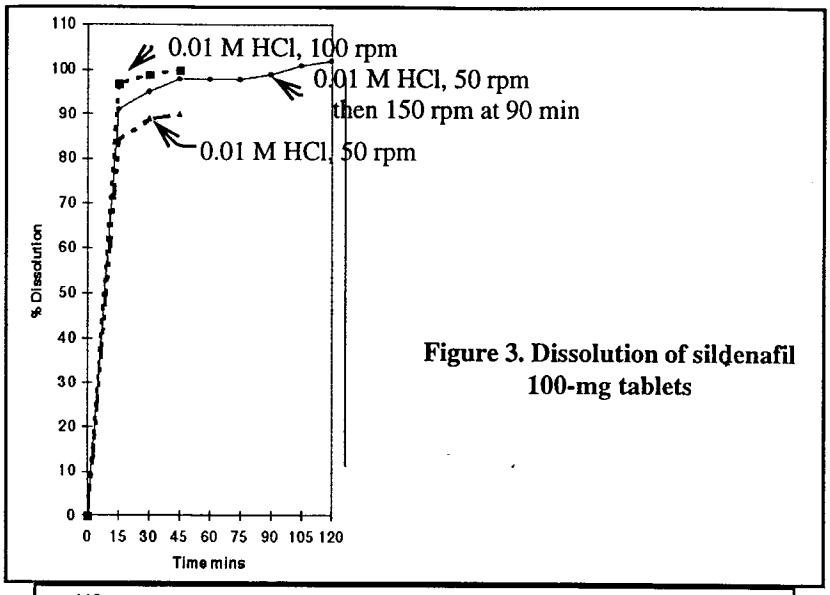

Figure 3. Dissolution of sildenafil 100-mg tablets

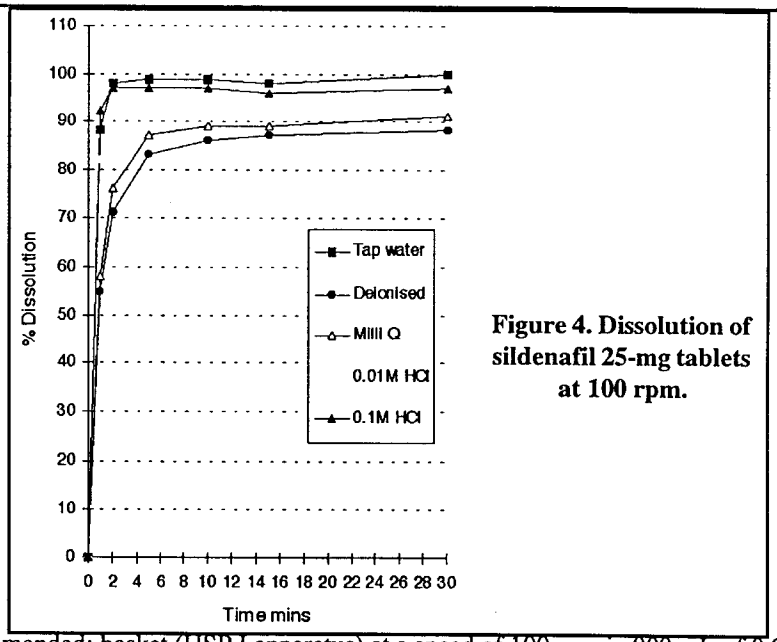

Figure 4. Dissolution of sildenafil 25-mg tablets at 100 rpm.

recommended: basket (USP I apparatus) at a speed of 100 rpm in 900 mL of 0.01 M HCl, and Q of at 15 minutes.

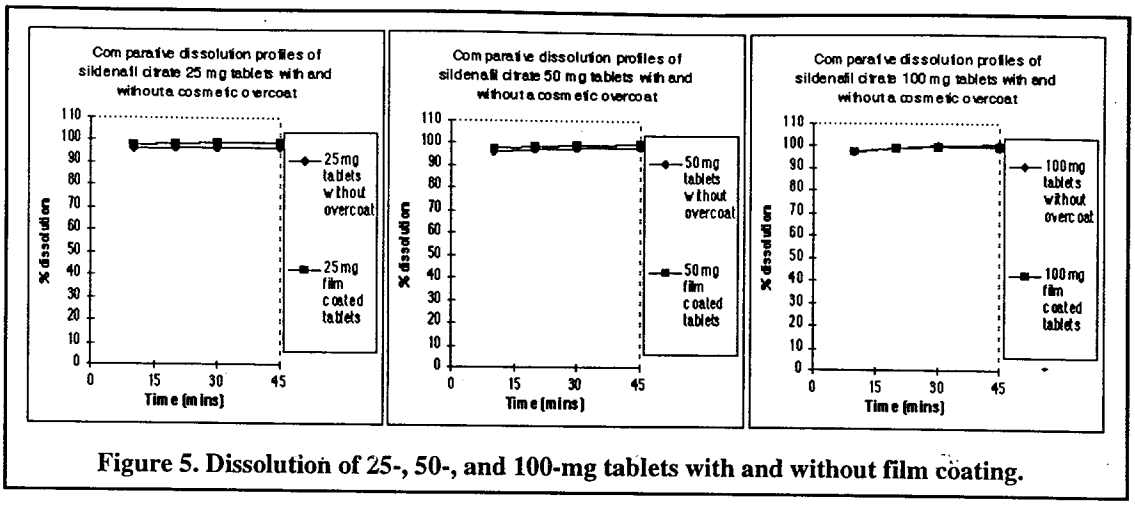

Figure 5. Dissolution of 25-, 50-, and 100-mg tablets with and without film coating.

6.9. Assay

In the vast majority of studies, an was used to measure the plasma concentrations of sildenafil and its metabolite. In a few studies a assay was used. Overall the analytical validation was satisfactory.

6.10. Comments

- The sponsor investigated the effects of sildenafil on the pharmacokinetics of tolbutamide. Valuable additional information on the pharmacokinetics of sildenafil in the presence of a competitive inhibitor CYP2C9 could have been obtained if they also assayed for sildenafil and its metabolite.
- The population pharmacokinetic analysis showed that concomitant administration of CYP3A4 inhibitors decreased the apparent oral clearance of sildenafil by only 14%. However, Study 148-234 showed there was a 182% increase in sildenafil exposure upon concomitant administration of erythromycin. These results would not have been predicted from the population analysis. The sponsor is requested to resolve the discrepancy between the results of the two analyses.
- In clinical study 148-102, the sponsor used a tablet formulation that is different in shape from the tablet used in the pivotal bioequivalence study to link the commercial tablet formulation with the formulations used in the pivotal clinical trials. The sponsor submitted dissolution data in 900 mL of 0.01 M HCl using a paddle speed of 50 rpm to show that the dissolution of this formulation is very rapid (>90% in 15 minutes) and is very similar to the commercial tablet formulation. Based on the submitted dissolution data, an in vivo bioavailability waiver is granted for the above clinical formulation (S00406AC and S00394AD).

6.11. Recommendation

The following dissolution method and specifications are recommended for sildenafil tablets: USP Apparatus I (basket) at a speed of 100 rpm and Q of n 15 minutes.