Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Section 8, pages 40-56

8. Integrated review of safety

8.1. Methodology

8.1.1. Deaths

For each death reported by the sponsor, the sponsor's narrative summary was compared with the case report form. The case report form was combed for indications of drug-relatedness of the immediate cause of death or associated problems.

8.1.2. Serious adverse events

The sponsor identified serious adverse events as those that were fatal, life-threatening, permanently disabling, resulted in or prolonged hospitalization, associated with congenital anomaly, cancerous, or resulted from overdose of study drug.

8.1.3. Withdrawals and other significant adverse events

8.1.3.1. Overall profile of withdrawals

Withdrawals were characterized by the primary associated event, as identified by the sponsor. The reviewers made no attempt to characterize other adverse events occurring in this sub-group, nor was any attempt made to recategorize the causes for withdrawal.

8.1.3.2. Adverse events associated with withdrawal

Adverse events associated with withdrawal were analyzed separately for the double-blind and open-label periods. Case report forms were examined for all adverse events identified by the sponsor as leading to withdrawal, to look for drug-relatedness or associated problems. Tables were generated by the reviewers for adverse events leading to withdrawal, organized by content-dependent categories, and including dosing exposure and demographic data.

8.1.3.3. Other significant adverse events

Common adverse events were analyzed separately for the double-blind and open-label periods. Dose-relatedness was assessed for common adverse events in placebo-controlled studies for which dosing information was available[1].

8.1.4. Other search strategies

Adverse events were reviewed on case report forms for deaths and withdrawals.

8.1.5. Adverse event incidence

8.1.5.1. Approach to eliciting adverse events in the development program

Protocols all contained provision for the periodic ascertainment of adverse events from subjects through non-directive questioning. There is no reason to suspect bias or inadequate reporting of adverse events with this methodology.

8.1.5.2. Appropriateness of adverse event categorization and preferred terms

Rates for common adverse events were determined solely by the sponsor's categorization. There is, therefore, some possibility that some events were scattered among terms allocated, perhaps inappropriately, to multiple body systems. Little effort was spent searching the safety data systematically for such abuses. Categorization of events by body system and by likelihood of being related to study drug was performed by the reviewers.

8.1.5.3. Identifying common and drug-related adverse events

Common adverse events in placebo-controlled studies were derived from the experience available electronically with the original submission.

8.1.5.4. Additional analyses

No additional analyses of adverse events were performed.

8.1.6. Laboratory findings

8.1.6.1. Extent of laboratory testing

Clinical chemistry, hematology, urinalysis, and ECG were all routinely performed at the beginning and end of blinded treatment periods in major studies. Testing was also performed at follow-up visits during open-label studies. This level of monitoring should be considered adequate for a drug for use in this population.

8.1.6.2. Selection of studies and analyses for drug-control comparisons

While serious event-related analyses covered all trial experience, analyses of trends in laboratory data focussed on previously identified collections of double-blind. placebo-controlled parallel-group studies.

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[1] Unabridged datasets were supplied only for Studies 148-102, 148-103, 148-363, and 148-364.

8.1.6.3. Standard analyses

8.1.6.3.1. Analyses focussed on central tendency and outliers

The reviewers undertook a staged approach to examination of laboratory data. The sponsor identified no clinically significant changes in central tendency. The reviewers screened data for subjects experiencing a significant shift from a normal baseline value. In a few cases, all lab values were reviewed for the few subjects demonstrating at least an excursion to a clinically significant value. Specific details are described in the various sections dealing with laboratory findings.

8.1.6.3.2. Withdrawals for laboratory abnormalities

Withdrawals for laboratory abnormalities are listed among withdrawals for other adverse events.

8.1.7. Vital signs

Vital signs were analyzed in the same manner as clinical laboratory data.

8.1.8. ECGs

ECGs were analyzed in the same manner as other clinical laboratory data.

8.1.9. Special studies

The sponsor conducted studies of effects of sildenafil on vision, on platelet aggregation and bleeding, and on blood pressure response when co-administered with nitroglycerin.

Drug interaction studies are discussed elsewhere.

8.1.10. Withdrawal phenomena

Withdrawal effects have not been studied formally.

8.1.11. Abuse potential

Although there are no evident effects on the central nervous system indicative of a risk of physical dependence, it can be supposed that sildenafil will be prescribed in a population with little objective need. Sildenafil is also likely to be see use in a population outside of the one for which it is prescribed.

8.1.12. Human reproduction data

All studies were conducted in a population at low risk of pregnancy.

There are no reports of women conceiving with partners on sildenafil.

8.1.13. Overdose experience

The sponsor's recommendation is for dosing not to exceed once daily, but in studies, some subjects exceeded that by amounts difficult to ascertain. Single doses up to 800 mg have been studied formally in normal volunteers.

8.2. Safety results

8.2.1. Deaths

Deaths occurring on study drug or within 30 days of receipt of study drug are listed in Table 29 below. There was only one death on placebo. Of 8 deaths on sildenafil, all were of a cardiovascular nature and most occurred in a setting of risk factors and medical history making the observed events plausibly not related to study drug. In no case did an investigator attribute death to study drug.

Table 29. Deaths on or within 30 days of study drug.

Study	Subject	Age	Race	Dose mg	Description
148-102	95220372	76	Cauc	Pcbo	History of diabetes and CHF. He died of self-inflicted gunshot wound on day 51.
148-104C	95110230	67	Cauc	100	History of diabetes, CHF, s/p aortic valve replacement. He died of multiple organ failure on day 51.
148-301	0090004	70	Cauc	40	Subject in angina study received 1 dose 11 days prior to emergency CABG. He died on day 14.
148-356	0780131	66	Cauc	10	History of smoking. He died on day 9 of presumed myocardial infarction. There was no autopsy.
148-363	1090178	66	Cauc	25	History of alcohol abuse, hypertension, hypercholesterolemia. He died of probable myocardial infarction on day 89.

Table 29. Deaths on or within 30 days of study drug. *(Continued)*

Study	Subject	Age	Race	Dose mg	Description
148-365	0950016	53	Cauc	100	No pertinent history. Died of myocardial infarction on day 17.
148-370	1390461	64	Cauc	Unk	History of arrhythmia (unspecified). He fell and suffered a cerebral hemorrhage and died of pulmonary sepsis on day 155.
148-365	0270007	62	Cauc	50	History of coronary artery disease. He died of myocardial infarction on day 104.
148-370	1540729	58	Cauc	50	He died of cardiac failure secondary to metastatic bladder carcinoma an unknown time after receiving study drug.
148-102C	95220009	57	Cauc	100	History of hypertension. He completed 6 months open-label and died of myocardial infarction 1 or 13 days after the last dose.

8.2.2. Withdrawals

8.2.2.1. Withdrawals for any cause

8.2.2.1.1. Withdrawals from placebo-controlled studies

Reasons for withdrawal from placebo-controlled studies are shown in Table 30 below. Lack of effectiveness (LOE) was the most common cause for withdrawal from placebo groups, particularly in longer-running studies. Adverse events (AE) and withdrawal of consent (With) were less than half as common in the placebo group. Lack of effectiveness was a much less common cause for withdrawal from sildenafil treatment groups (about 27% as common). Adverse events as reasons for withdrawal had the same incidence in placebo and sildenafil treatment groups. Laboratory abnormalities, loss to follow-up, 'other' (Oth), protocol violations, and withdrawal of consent were all more common on placebo than on sildenafil. There were 3 deaths on sildenafil versus none on placebo, and 3 subjects withdrawn from sildenafil because they were randomized in error versus none on placebo. Overall, 16% of subjects randomized to placebo and 9% of subjects randomized to sildenafil withdrew for any reason from placebo-controlled studies, with much of the difference between groups being attributable to differences in rates of withdrawal for lack of effectiveness, particularly in longer-running studies.

Table 30. Withdrawals from placebo-controlled studies[a].

	Placebo											Sildenafil										
	N	AE	Death	LOE	Lab	LFU	Oth	Viol	With	Rand	Any	N	AE	Death	LOE	Lab	LFU	Oth	Viol	With	Rand	Any
148-101/101B	83	6	—	1	1	—	2	—	6	—	16	333	5	1	6	3	3	8	4	11	—	41
148-102	216	5	—	11	1	6	3	4	6	—	36	316	8	—	5	2	6	3	4	3	—	31
148-103	166	4	—	3	—	2	2	1	1	—	13	163	3	—	1	—	3	—	—	2	—	9
148-104	132	1	—	1	3	—	1	—	5	—	11	136	1	—	1	—	1	—	—	2	—	5
148-106	122	4	—	8	2	2	1	1	—	—	18	375	16	—	7	2	5	5	3	4	1	43
148-353	95	4	—	—	—	4	—	—	—	1	9	256	13	—	4	3	2	3	—	—	—	25
148-355	43	1	—	—	—	1	—	1	—	—	3	44	—	—	—	—	1	—	1	—	—	2
148-359	54	2	—	1	—	2	4	1	1	—	11	57	—	—	1	—	—	—	—	—	—	1
148-361	59	1	—	—	—	—	—	2	2	—	5	195	2	—	1	1	—	—	2	3	1	10
148-363	156	5	—	54	3	5	4	2	4	—	77	159	8	2	13	2	4	2	3	—	1	35
148-364	127	1	—	6	—	2	—	—	2	—	11	387	6	—	3	1	3	1	2	3	—	19
148-367	89	2	—	—	1	—	1	—	—	—	4	89	5	—	—	—	1	—	—	—	—	6
Total	1342	36	0	85	11	24	18	12	27	1	214	2510	67	3	42	14	29	22	19	28	3	227
Incidence (%)	—	2.7	—	6.3	0.8	1.8	1.3	0.9	2.0	—	16	—	2.7	0.1	1.7	0.6	1.2	0.9	0.8	1.1	0.1	9.0

a. AE = adverse event; LOE = lack of effectiveness; Lab = laboratory abnormality; LFU = loss to follow-up; Viol = protocol violation; With = withdrawal of consent; Rand = randomization in error.

8.2.2.1.2. Withdrawals from open-label extensions

Reasons for withdrawal from open-label studies are shown in Table 31 below. The incidence of withdrawals for lack of effectiveness was higher during open-label studies than during placebo-controlled studies, but the incidence is very low and the period of exposure is much longer for open-label studies. Overall, only 10% of subjects withdrew for any reason from open-label studies.

Table 31. Withdrawals from open-label studies.

	Sildenafil										Sildenafil								
	N	AE	Death	LOE	Lab	LFU	Oth	Viol	With		N	AE	Death	LOE	Lab	LFU	Oth	Viol	With
148-101C	337	14	1	29	2	7	7	1	7	148-354B	148	6	—	2	—	5	5	—	1
148-102C	402	—	—	15	1	1	1	1	4	148-354C	32	1	—	6	2	8	—	—	4
148-103C	225	5	—	8	1	—	—	1	3	148-361O	227	1	—	—	4	—	—	—	2
148-104C	185	3	—	16	—	—	1	1	1	148-366	203	—	—	7	1	1	—	—	—
148-105	54	1	—	—	—	—	—	—	—										
148-350	16	1	—	—	—	—	—	—	—	Total	2137	41	1	94	13	27	19	7	26
148-354A	308	9	—	11	2	5	5	3	4	Incidence (%)		1.9	—	4.4	0.6	1.3	0.9	0.3	1.2

8.2.2.2. Withdrawals for adverse events

8.2.2.2.1. Withdrawals from placebo-controlled studies

Subjects who discontinued from double-blind, placebo-controlled studies because of adverse event or adverse laboratory values are shown in Table 32 below. Dosing and evaluation of events as serious or not was available from all studies; where the dose of a subject randomized to sildenafil was not available from the sponsor's integrated safety database, the value is shown below as '>0' and where the evaluation of seriousness was unavailable, the table shows '?'. Event categories were established by clinical importance or apparent frequency in the data; some subjects have events match more than one category and are listed multiple times. Lines are not replicated in the 'other' category. For some categories, the available CRFs were scanned for pertinent baseline findings or medical history.

Table 32. Adverse events leading to withdrawal from placebo-controlled studies.

Study	PID	Dose	Age	Race	Days	SAE	Related	Description
Cardiovascular—arrhythmia								
101	95000036	0	68	White	151	?	N	Deep thrombophlebitis, atrial fibrillation
101	95030028	0	62	White	50	?	Y	Palpitation; history of MI
102	95270566	0	64	Black	43	Y	N	Atrial fibrillation; no relevant history
353	630409	0	43	White	1	?	Y	Palpitation, anxiety; no relevant history
363	1260330	0	53	Asian	81	N	N	Ventricular extrasystoles; diabetes diagnosed at screening
106	95670251	>0	70	White	57	?	N	Atrial fibrillation; history of MI, hypertension, arrhythmia
363	1160280	>0	70	White	81	?	N	Cardiomyopathy; arrhythmia; agitation, arthralgia
363	1090178	25	65	White	92	Y	N	Cardiac arrest; history of hypertension
Cardiovascular—blood pressure								
101	95020385	0	64	White	30	?	N	Hypertension
106	95720414	>0	63	Other	41	?	N	Hypotension; asthenia; vomiting; diarrhea
353	550371	>0	49	White	27	?	N	Vasodilation
363	1260328	>0	62	White	58	?	Y	Vasodilation; abdominal pain
363	1320081	100	59	White	126	N	N	Hypertension; history of same
Cardiovascular—myocardial infarction								

Table 32. Adverse events leading to withdrawal from placebo-controlled studies. *(Continued)*

Study	PID	Dose	Age	Race	Days	SAE	Related	Description
103	95000163	0	63	White	29	Y	N	Myocardial infarction, stroke; history of CABG, peripheral vascular disease, hypertension
103	95070035	0	64	White	56	Y	N	Myocardial infarction, angioplasty; no relevant history
106	95610018	0	55	White	68	?	N	Myocardial infarct; history of hypertension, CAD, angina, diabetes, hyperlipidemia
106	95780138	0	59	White	59	?	N	Respiratory tract infection, MI; history of hypertension and smoking
355	850113	0	62	White	29	?	Y	Respiratory tract infection, MI; no relevant history
361	1020009	>0	68	White	45	?	N	Myocardial infarct; history of diabetes
102	95050319	25	64	White	86	Y	N	Myocardial infarction; no relevant history
102	95170401	50	63	White	192	Y	N	Myocardial infarction; no relevant history
Cardiovascular—other								
102	95220372	0	76	White	15	N	N	Shortness of breath, heart failure; history of myocardial infarction, CABG, and diabetes
106	95740242	0	62	White	32	?	N	Anxiety, CAD, dyspnea
101	95210164	>0	49	White	113	?	N	Hemoptysis; cardiomyopathy; infection
106	95670251	>0	70	White	57	?	N	Worsening heart failure; pharygitis; history of hypertension, MI, arrhythmia, CHF
363	1190322	>0	64	White	92	?	N	Cerebrovascular disorder; history of diabetes and TIA
364	1440268	>0	76	White	73	?	N	Cerebrovascular disorder, AV block; history of hypertension
363	1120007	50	74	White	48	N	Y	ECG changes; no relevant history
102	95390139	100	63	White	1	Y	N	Coronary artery disease; history of hypertension, myocardial infarction
103	95450321	100	57	White	57	Y	N	Angina; history of peripheral vascular disease, hypertension
363	1160280	100	70	White	81	Y	N	Cardiomyopathy, arrhythmia; history of peripheral vascular disease
LFT								
101	95080249	0	47	Black	36	?	Y	SGOT, SGPT increased; no relevant history
101	95100088	0	68	White	114	?	N	Hepatoma, back pain
102	95350454	0	43	White	21	N	Y	Increased LFTs; no relevant history
106	95810153	0	65	White	31	?	Y	SGOT, SGPT increased; no relevant history
363	1250374	0	60	White	73	?	Y	SGPT, SGOT, AlkP increased; no relevant history
363	1250374	0	60	White	73	N	Y	Liver enzyme elevation; no relevant history
363	1270108	0	58	White	143	N	N	Liver enzyme elevation; no relevant history
367	1630409	0	36	White	25	?	Y	Skin disorder; SGOT, SGPT increased; no relevant history
101	95190375	>0	55	White	13	?	Y	Liver function tests abnormal; headache
353	640358	>0	63	White	3	?	N	BUN, AlkP, SGPT, SGOT increased; no relevant history
102	95290191	25	50	White	98	N	N	Increased LFTs; history of peripheral vascular disease
102	95370156	50	55	Black	95	N	Y	Increased LFTs; no relevant history
364	1460269	100	53	White	70	N	N	Liver enzyme elevation, attributed to alcohol; history of manic-depression, but not alcohol abuse
Headache								
102	95220247	0	70	White	18	N	Y	Nausea, headache
103	95000202	0	66	White	30	N	Y	Headache, dizziness; no relevant history
353	100180	0	59	White	28	?	Y	Headache
363	1060054	0	58	White	28	N	Y	Headache; no relevant history
367	1650393	0	44	White	25	?	Y	Headache, myalgia
101	95190375	>0	55	White	13	?	Y	Liver function tests abnormal; headache
101	95200154	>0	73	White	4	?	Y	Emotional lability; headache; nervousness
106	95410089	>0	58	White	13	?	Y	Diarrhea; headache; abnormal vision

Table 32. Adverse events leading to withdrawal from placebo-controlled studies. *(Continued)*

Study	PID	Dose	Age	Race	Days	SAE	Related	Description
106	95670264	>0	62	White	14	?	Y	Headache; asthenia; abdominal pain
106	95680385	>0	79	White	6	?	Y	Bloody diarrhea; headache
106	95680417	>0	66	White	15	?	Y	Headache
106	95690312	>0	68	White	5	?	Y	Abnormal vision; vomiting; lacrimal disorder; headache
106	95740247	>0	62	White	28	?	Y	Headache; asthenia; dyspepsia; vasodilation
106	95740297	>0	46	White	28	?	Y	Anorexia; headache; abnormal vision; rhinitis; eructation
106	95800083	>0	65	White	29	?	N	Headache; hyperglycemia
106	95800142	>0	54	White	8	?	N	Gum hemorrhage; vasodilation; headache; nausea
353	260186	>0	56	White	29	?	N	Flu syndrome; headache
353	270034	>0	24	White	28	?	Y	Headache; hypertonia; dyspepsia; pain
353	310101	>0	54	White	15	?	Y	Headache; vasodilation
353	310104	>0	49	Asian	10	?	Y	Respiratory disorder; headache
353	360021	>0	54	White	14	?	Y	Eye pain; myalgia; headache
353	640354	>0	44	White	29	?	Y	Vasodilation; headache; pharyngitis; rhinitis; epistaxis
353	670390	>0	54	White	14	?	Y	Nausea; headache; somnolence; respiratory disorder
363	1080247	>0	70	White	13	?	Y	Headache; abnormal vision
363	1110213	>0	55	White	48	?	Y	Insomnia; headache
363	1220302	>0	52	White	8	?	Y	Dizziness; headache
364	1460269	>0	53	White	70	?	N	Liver function tests abnormal; headache
367	240105	>0	32	White	18	?	N	Headache
367	1650391	>0	40	White	7	?	Y	Nausea; headache
367	1800058	>0	48	White	9	?	Y	Nausea; dyspepsia; vasodilation; headache
364	160490	>0	70	White	5	?	Y	Headache
364	750613	>0	65	Black	2	?	N	Dyspepsia; diarrhea; flatulence; headache; vomiting; nausea; abdominal pain
363	1080247	25	70	White	13	N	Y	Headache, visual disturbance; no relevant history
363	1220302	25	52	White	8	N	Y	Headache, dizziness; no relevant history
363	1110213	50	55	White	48	N	Y	Headache; no relevant history
363	1190322	50	64	White	92	Y	N	CVA, headache; no relevant history
102	95190117	100	41	White	94	N	Y	Headache, heartburn; no relevant history
102	95370159	100	72	White	4	N	Y	Headache
103	95070087	100	72	White	50	N	Y	Headache, flushing; history of hypertension
364	160490	100	70	White	5	N	Y	Headache, new onset diabetes; no relevant history
Visual disturbance								
102	95330219	0	73	White	34	N	N	Retinal changes; history and in-study atrial fibrillation
106	95690312	>0	68	White	5	?	Y	Abnormal vision; vomiting; lacrimal disorder; headache
106	95740297	>0	46	White	28	?	Y	Anorexia; headache; abnormal vision; rhinitis; eructation
363	1080247	>0	70	White	13	?	Y	Headache; abnormal vision
106	95800084	>0	59	White	15	?	N	Retinal hemorrhage
106	95800088	>0	53	White	8	?	Y	Abnormal vision
353	310102	>0	29	White	8	?	N	Abnormal vision
363	1080247	25	70	White	13	N	Y	Headache, visual disturbance; no relevant history
Other								
101	95000038	0	60	White	120	?	N	Chest pain

Table 32. Adverse events leading to withdrawal from placebo-controlled studies. *(Continued)*

Study	PID	Dose	Age	Race	Days	SAE	Related	Description
101	95210255	0	42	Black	28	?	Y	Pain
102	95250463	0	66	White	57	Y	N	Mesothelioma, stroke; history of hypertension, diabetes
103	95400300	0	67	White	71	Y	N	Possible TIA; no relevant history
104	95360115	0	40	White	1	?	N	Npn increased
104	95480148	0	70	White	17	?	N	Hyperglycemia
106	95770197	0	54	White	66	?	N	Varicose vein, bilirubinemia
353	100177	0	54	White	14	?	Y	Diarrhea
353	330089	0	35	White	19	?	Y	Psoriasis
359	270032	0	54	White	28	?	N	Procedure
359	600070	0	63	White	62	?	N	Pancreatitis, abdominal pain
361	1030253	0	62	White	68	?	N	Procedure (medical/surgical/health service)
363	1130297	0	57	White	30	?	N	Arthralgia, anemia, bronchitis, gastritis
363	1080245	0	59	White	73	Y	N	<<<AE page missing.>>
363	1150254	0	60	White	17	Y	N	Prostate cancer
363	1180309	0	33	White	1	N	N	"Aggravation of" alcohol abuse; no relevant history
363	1130297	0	57	White	30	N	N	Anemia; present from baseline
364	1520233	0	58	White	23	Y	N	Major depression; history of depression
101	95000039	>0	65	White	96	?	N	Carcinoma
101	95030030	>0	60	Black	65	?	N	Leukopenia
101	95170123	>0	46	White	87	?	N	Respiratory disorder, arthralgia, esoghageal ulcer
101	95170355	>0	66	White	94	?	N	Thrombocytopenia
101	95200155	>0	72	White	76	?	N	Allergic reaction
101	95200157	>0	52	White	112	?	N	Respiratory tract infection; lymphoma-like reaction; abscess; lymphadenopathy
106	95670241	>0	78	White	11	?	Y	Asthenia; myalgia; tachycardia; pain
106	95810144	>0	59	White	13	?	N	Arteriosclerosis
353	240171	>0	60	White	15	?	Y	Arthralgia
353	240171	>0	60	White	15	?	Y	Abdominal pain
353	290055	>0	63	White	29	?	Y	Dyspepsia
353	340113	>0	49	White	14	?	N	Asthenia; back pain; weight loss; nausea
353	360026	>0	61	White	15	?	Y	Pain
353	520211	>0	63	White	14	?	Y	Abdominal pain; leg cramps
353	560279	>0	69	White	22	?	Y	Kidney function abnormal; insomnia; anxiety
361	1020009	>0	68	White	45	?	N	Joint disorder
361	1030286	>0	61	White	59	?	N	Dyspepsia
363	1090177	>0	68	White	195	?	N	Accidental fall
363	1210354	>0	65	White	4	?	N	Hyperglycemia
363	1220382	>0	57	White	4	?	Y	Nausea; diarrhea
364	630018	>0	54	White	3	?	Y	Abdominal pain
364	630018	>0	54	White	3	?	Y	Vomiting; dyspepsia
364	1440254	>0	79	White	58	?	N	Chest pain
367	240105	>0	32	White	18	?	N	Skin ulcer
367	240104	>0	45	White	4	?	Y	Conjunctivitis; headache
367	1590133	>0	38	White	20	?	N	Abdominal pain; hypesthesia

Table 32. Adverse events leading to withdrawal from placebo-controlled studies. *(Continued)*

Study	PID	Dose	Age	Race	Days	SAE	Related	Description
102	95110054	25	48	White	174	Y	N	Need for concomitant medication; history of hypertension, myocardial infarction, and angioplasty
102	95270399	25	67	White	1	N	Y	Nausea, vomiting
363	1220382	25	57	White	4	N	Y	Nausea, diarrhea
363	1210354	25	65	White	4	N	N	Hyperglycemia; history of diabetes
102	95170103	50	64	White	13	N	Y	Back and leg ache; no relevant history
103	95400284	50	58	White	10	Y	N	Cerebral infarct; no relevant history
363	1090177	50	68	White	195	Y	N	Accidental death
364	1440268	50	76	White	73	Y	N	TIA; history of hypertension
363	1260328	100	62	White	58	N	Y	Hot flushes, stomach ache
364	630018	100	54	White	3	N	Y	Abdominal pain, vomiting
364	750613	100	65	Black	2	N	N	Subacute intestinal obstruction; no relevant history
364	1380438	100	64	White	58	Y	N	Hepatic metastasis of bladder cancer
364	1440254	100	79	White	58	N	N	Chest (muscle) pain; history of asymptomatic supraventricular arrhythmia

8.2.2.2.2. Withdrawals from open-label extensions

Adverse events or laboratory findings associated with or contributing to withdrawal from open-label studies are shown in Table 33 below. This table is similar to Table 32 on page 43, but for none of these trials was the dosing information or an evaluation of seriousness easily determined from the electronic data, so these fields are omitted.

Table 33. Adverse events leading to withdrawal from open-label studies

Study	PID	Age	Race	Days	SAE	Description
Cardiovascular						
101C	95080079	60	White	148	Yes	Abnormal vision; dyspnea; vasodilation
101C	95070326	60	White	158	Yes	Rhinitis; dyspepsia; vasodilation
101C	95110232	58	White	83	No	Conjunctivitis; angina pectoris; insomnia; rectal hemorrhage; vasodilation
105	95060053	24	Black	1	Yes	Vertigo; vasodilation
104C	95470185	57	White	12	Yes	Dizziness; hypertension; headache
101C	95230285	60	White	185	No	Procedure (medical/surgical/health service); CAD
354B	00956162	68	White	355	No	Myocardial infarct
LFT						
101C	95210169	68	White	149	No	SGOT, AlkP increased
103C	95000157	49	White	30	No	Alkaline phosphatase increased
354A	00290057	61	White	336	No	Arthritis; convulsion; AlkP increased
354C	00248018	63	White	61	Yes	Liver function tests abnormal
354C	00608071	48	White	179	No	Liver function tests abnormal; flu syndrome
366	1150260	47	White	24	Yes	Liver function tests abnormal
Headache						
101C	95050318	73	Asian	79	Yes	Headache, dizziness, prostatic disorder, abnormal vision
101C	95110237	61	White	89	Yes	Headache; rhinitis
102C	95000286	75	White	15	No	Sweating; dizziness; lab test abnormal; headache
103C	95070065	64	White	28	Yes	Headache
103C	95110155	64	White	57	Yes	Herpes simplex; headache
103C	95430169	68	White	28	Yes	Headache; abdominal pain
104C	95470185	57	White	12	Yes	Dizziness; hypertension; headache

Table 33. Adverse events leading to withdrawal from open-label studies

Study	PID	Age	Race	Days	SAE	Description
354A	00240020	42	White	6	Yes	Dyspepsia; headache; lacrimation disorder; voice alteration; respiratory disorder
354A	00580141	53	White	49	Yes	Headache; dyspepsia; respiratory tract infection
354C	00608067	55	White	110	Yes	Headache
Visual disturbance						
101C	95050318	73	Asian	79	Yes	Headache, dizziness, prostatic disorder, abnormal vision
101C	95080079	60	White	148	Yes	Abnormal vision; dyspnea; vasodilation
103C	95180011	56	White	54	Yes	Abnormal vision; vasodilation; headache
104C	95070012	75	White	10	Yes	Pain; abnormal vision
354A	00670400	36	White	50	Yes	Diarrhea; abnormal vision; abdominal pain
Other						
101C	95020018	67	White	82	No	Carcinoma
101C	95090208	60	White	124	No	Lymphadenopathy; lymphoma-like reaction
101C	95100418	77	White	121	No	Procedure (medical/surgical/health service)
101C	95130101	72	White	175	No	Carcinoma; accidental injury
101C	95140113	64	Other	169	No	Respiratory tract infection
101C	95140113	64	Other	169	No	Hyperglycemia; insomnia; constipation; pancreatitis; gastrointestinal carcinoma; dyspepsia; anorexia; hernia; cholelithiasis
101C	95150198	65	White	192	No	Dyspnea; lung edema
101C	95220177	72	White	148	Yes	Dizziness; pain
101C	95220276	73	White	10	No	Deafness; encephalopathy; dizziness
350	100008	42	White	2	Yes	Dyspepsia
354A	00240020	42	White	6	Yes	Dyspepsia; headache; lacrimation disorder; voice alteration; respiratory disorder
354A	00242119	63	White	73	Yes	Flu syndrome; hemorrhage
354A	00290056	57	White	66	No	Dizziness
354A	00480226	45	White	261	No	Seborrhea
354A	00620334	66	White	130	No	Skin melanoma
354A	00620415	45	Other	110	No	Leukopenia; gastritis; dyspepsia
354A	00640360	61	White	113	No	Cerebral thrombosis
354A	00690250	65	White	24	Yes	Abdominal pain
354B	00776040	57	White	352	Yes	Flu syndrome; somnolence; angina pectoris; headache; respiratory tract infection
354B	00776246	51	White	56	Yes	Rhinitis; pain
354B	00786106	47	White	239	No	Abdominal pain
354B	00786106	47	White	239	No	Testis disorder; carcinoma; back pain
354B	B0087620	69	White	266	No	Carcinoma
361O	01030249	49	White	84	Yes	Sinusitis; vasodilation

8.2.3. Common adverse events

8.2.3.1. Relationship to dose

Dose-relatedness of common adverse events was investigated for the 4 placebo-controlled studies for which dosing information was available—Studies 102, 103, 363, and 364. The denominators for incidence were the numbers of subjects exposed to a dose; because three of these studies were titration studies, many subjects contributed to the denominators for more than one active dose level.

Dose-relatedness of adverse events is shown in Table 34 below. Headache, dyspepsia, rhinitis, vision abnormalities, arthralgia, pain, abdominal pain, and rash were plausibly dose-related.

Table 34. Dose-relatedness of common adverse events in placebo-controlled studies.

	Placebo N=665		Sildenafil 25 mg N=394		50 mg N=519		100 mg N=439			Placebo N=665		Sildenafil 25 mg N=394		50 mg N=519		100 mg N=439	
	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%
Headache	58	8.7	81	21	122	24	126	29	Dizziness	13	2.0	15	3.8	16	3.1	14	3.2
Vasodilation	9	1.4	69	18	103	20	89	20	Arthralgia	17	2.6	6	1.5	9	1.7	14	3.2
Dyspepsia	16	2.4	15	3.8	42	8.1	51	12	Pain	10	1.5	6	1.5	9	1.7	19	4.3
Respir tract infect	48	7.2	14	3.6	18	3.5	18	4.1	Sinusitis	23	3.5	4	1.0	6	1.2	11	2.5
Back pain	18	2.7	16	4.1	21	4.0	11	2.5	Abdominal pain	11	1.7	4	1.0	6	1.2	14	3.2
Accident	27	4.1	10	2.5	17	3.3	12	2.7	Diarrhea	14	2.1	9	2.3	6	1.2	9	2.1
Rhinitis	17	2.6	7	1.8	16	3.1	23	5.2	Rash	13	2.0	4	1.0	7	1.3	12	2.7
Flu syndrome	23	3.5	17	4.3	1	2.1	11	2.5	Nausea	4	0.6	8	2.0	9	1.7	12	2.7
Abnormal vision	5	0.8	5	1.3	12	2.3	38	8.7									

8.2.3.2. Overall incidence

The sponsor and the reviewers agree that the description of the incidence of adverse events most likely to mirror any subsequent experience in clinical practice would be derived from placebo-controlled flexible-dosing studies[2]. Table 35 below lists events by body system with an incidence of at least 1% in the combined sildenafil treatment group.

Table 35. Percentage of subjects with common adverse events in flexible-dosing studies.

	Placebo N=725	Sildenafil N=734		Placebo N=725	Sildenafil N=734
Any	41	60	Musculoskeletal	4.5	5.4
General	15	26	Arthralgia	1.5	2.0
Headache	3.9	16	Myalgia	1.0	1.2
Flu syndrome	2.9	3.3	Nervous system	5.2	9.3
Back pain	1.7	2.2	Dizziness	1.2	2.2
Abdominal pain	1.0	1.5	Nervousness	—	1.8
Asthenia	0.6	1.4	Hypertonia	0.6	1.6
Infection	0.2	1.2	Respiratory	11	13
Pain	1.0	1.1	Rhinitis	1.5	4.2
Accident	1.7	1.1	Respir tract infec	5.4	4.2
Cardiovascular	4.1	14	Respiratory disorder	0.8	1.9
Vasodilation	0.7	11	Pharyngitis	1.4	1.4
Gastrointestinal	6.6	14	Skin	4.1	5.4
Dyspepsia	1.7	6.5	Rash	1.4	2.2
Diarrhea	1.0	2.6	Special sense	1.4	6.0
Nausea	0.4	1.2	Abnormal vision	0.4	2.7
Tooth disorder	0.8	1.1	Urogenital	5.1	7.1
Hematologic	0.8	0.8	Urinary tract infec	1.5	3.1
Metabolic/nutritional	1.9	2.2	Prostate disorder	1.0	1.2

[2] Studies 148-103, 148-104, 148-355, 148-359, 148-363, and 148-367.

8.2.4. Laboratory data

8.2.4.1. Hepatic function

Laboratory abnormalities pertaining to hepatic function were screened by identification of subjects in placebo-controlled studies who had bilirubin, SGOT, SGPT, or alkaline phosphatase within normal limits at baseline but increased 2-fold from baseline at study end. For such subjects, bilirubin, SGOT, SGPT, alkaline phosphatase, albumin, and total protein values were abstracted for further examination. Subjects were then classified as having abnormalities limited to bilirubin only, or abnormalities (greater than 2-fold increase from baseline) in enzymes as well.

The incidence of hepatic function abnormalities is shown in Table 36 below. Most of the recorded abnormalities were isolated increases in bilirubin, SGOT, or SGPT. Only 2 subjects[3], both on sildenafil, had as much as a doubling of alkaline phosphatase. In placebo-controlled studies, the rates and severity of laboratory abnormalities pertaining to hepatic function were similar in placebo and active treatment groups.

Table 36. Hepatic function abnormalities in placebo-controlled studies.

	Placebo N=1342			Sildenafil N=2510		
	n	%	-fold max	n	%	-fold max
Bilirubin only	22	1.6	2.1	35	1.4	4.0
Enzymes						
1	23	1.7	19	46	1.8	17
2	6	0.4		9	0.4	
3	—	—		—	—	

8.2.4.2. Renal function

Laboratory abnormalities pertaining to renal function were screened by identification of subjects in placebo-controlled studies who had BUN or creatinine within normal limits at baseline but increased 1.2-fold from baseline at study end. For such subjects, BUN and creatinine values were abstracted for further examination.

Only 2 subjects were identified as having potentially clinically significant increases in BUN or creatinine during placebo-controlled studies. One subject on placebo[4] had no change in creatinine (0.81 mg/dL at baseline and 0.83 at study end) but BUN went from 50 to 114. One subject on sildenafil[5] progressed from a creatinine of 1.1 to 1.5 mg/dL; BUN was 20 at study end.

8.2.4.3. Electrolytes, hematology, etc.

Significant changes in electrolytes, creatine kinase, and hematologic parameters were assessed by counting subjects on placebo and sildenafil with fractional shifts from baseline exceeding a parameter-specific amount. The thresholds were chosen, in part to detect a change of potential clinical significance and in part to select a small percentage of placebo subjects to optimize detecting a sildenafil-placebo difference.

Potentially clinically significant shifts in electrolytes and creatine kinase during placebo-controlled studies are shown in Table 37 below. Shifts in hematologic parameters are shown in Table 38 below. Of these, the only laboratory parameter for which further investigation appeared to be appropriate was calcium: there is at least a trend for subjects on sildenafil to be less likely to have an increase in calcium and more likely to show a decrease.

Because of the apparent trend for a reduction in calcium in the preceding analysis, a second analysis was undertaken to look for systematic difference in calcium levels as

3. Study 101 subject 95020019 and study 102 subject 95000286.
4. Study 359 subject 700140.
5. Study 101 subject 95110096.

Table 37. Potentially clinically significant shifts in electrolytes in placebo-controlled studies.

		Placebo N=1342		Sildenafil N=2510				Placebo N=1342		Sildenafil N=2510	
		n	%	n	%			n	%	n	%
Sodium	↑5%	7	0.5	5	0.2	Calcium	↑10%	40	3.0	51	2.0
	↓5%	7	0.5	10	0.4		↓10%	17	1.3	68	2.7
Potassium	↑10%	126	9.4	252	10	Creatine kinase	↑10%	192	14	364	15
	↓10%	137	10	268	11		↓10%	191	14	401	16

Table 38. Potentially clinically significant shifts in hematologic parameters in placebo-controlled studies.

		Placebo N=1342		Sildenafil N=2510				Placebo N=1342		Sildenafil N=2510	
		n	%	n	%			n	%	n	%
Hematocrit	↑10%	34	2.5	63	2.5	WBC	↑50%	74	5.5	114	4.5
	↓10%	59	4.4	134	5.3		↓50%	9	0.5	31	1.2
							↓75%	2	0.1	3	0.1
Hemoglobin	↑10%	30	2.2	71	2.8	Neutrophil	↑50%	114	8.9	217	8.6
	↓10%	21	1.6	34	1.4		↓50%	25	1.9	47	1.9
							↓75%	5	0.4	7	0.3
RBC	↑10%	78	5.8	291	12	Platelets	↓50%	2	0.1	2	0.1
	↓10%	41	3.1	65	2.6		↓75%	—	—	—	—

a function of dose. Because dose information was not available in the integrated datasets, this analysis was performed on a dataset formed from laboratory data from the 4 placebo-controlled studies[6] for which full data were available. The analysis used the sponsor-identified baseline values and the last on-treatment value available for each subject, ignoring differences in the period of follow-up specified in the protocol design. The result is shown in Table 39 below. There is no evidence of an effect on mean calcium levels at any dose, and no dose-related trend.

Table 39. Relationship between dose at calcium level (Studies 102, 103, 363, and 364).

	Placebo N=1052	Sildenafil (mg) 25 N=288	50 N=360	100 N=608
Baseline	9.1±0.5	9.1±0.5	9.0±0.4	9.1±0.5
On treatment	9.2±0.4	9.1±0.5	9.2±0.4	9.2±0.4
Range	8.2–11.7	6.9–10.6	8.1–10.2	8.4–10.4

8.2.4.4. Vital signs

The sponsor evaluated median changes in vital signs in placebo-controlled phase II and II studies together and then looking at median changes in subjects on anti-anginal drugs—nitrates, β-blockers, calcium channel blockers, and potassium channel activators. These results are summarized in Table 40 below.

The reviewers computed mean changes in systolic and diastolic pressures and in pulse rate, for subjects in placebo-controlled studies. They also plotted vital signs at study

6. Studies 102, 103, 363, and 364.

Table 40. Summary of median changes in vital signs in placebo-controlled studies.

		All placebo-controlled				All placebo-controlled				All placebo-controlled			
		Placebo		Sildenafil		Placebo		Sildenafil		Placebo		Sildenafil	
		Base	Δ	Base	Δ	Base	Δ	Base	Δ	Base	Δ	Base	Δ
Sitting	N	1187		2200		187		353		471		847	
	Sys	130	0	130	0	140	0	140	-4	135	0	137	0
	Dias	80	0	80	0	82	0	82	0	80	0	80	0
	Pulse	72	0	72	0	72	0	72	0	72	0	74	0
Standing	N	16		16		—		—		—		—	
	Sys	116	0	118	-6	—	—	—	—	—	—	—	—
	Dias	80	-1	80	0	—	—	—	—	—	—	—	—
	Pulse	72	7	79	4	—	—	—	—	—	—	—	—
Supine	N	54		55		—		—		—		—	
	Sys	125	0	128	-3	—	—	—	—	—	—	—	—
	Dias	80	0	80	0	—	—	—	—	—	—	—	—
	Pulse	70	0	68	-1	—	—	—	—	—	—	—	—

end against baseline values, for these same studies, to look for outliers. These analyses (not shown here) are consistent with the sponsor's analyses of median changes; any such effects are small. This result however, must be interpreted in the context that end-of-study measurements were likely often made many hours or days after the last dose of study drug. Other data, discussed in section 8.2.5.1 on page 54, is indicative of a potentially clinically significant effect of sildenafil on blood pressure.

8.2.4.5. ECG

Electrocardiograms were obtained within 24 hours of a dose in phase III Studies 148-102 and 148-106, which exposed subjects to doses from 25 to 200 mg. ECGs were obtained 40 minutes after dosing subjects receiving intravenous sildenafil in Study 148-203. Studies 148-001, 148-004, 148-201, and 148-201A exposed 4 to 10 subjects per dose to doses ranging from 1.25 to 800 mg, with ECGs obtained 1 hour after dosing, near the time of expected peak plasma levels. Data from the latter collection of studies are shown in Figure 6 below. The figure and the data from the study with intravenous administration are consistent with there being a small, clinically insignificant, dose-related effect of sildenafil on heart rate. None of the study designs permit comment upon the duration of this effect, other than it being undetectable at 24 hours after dosing.

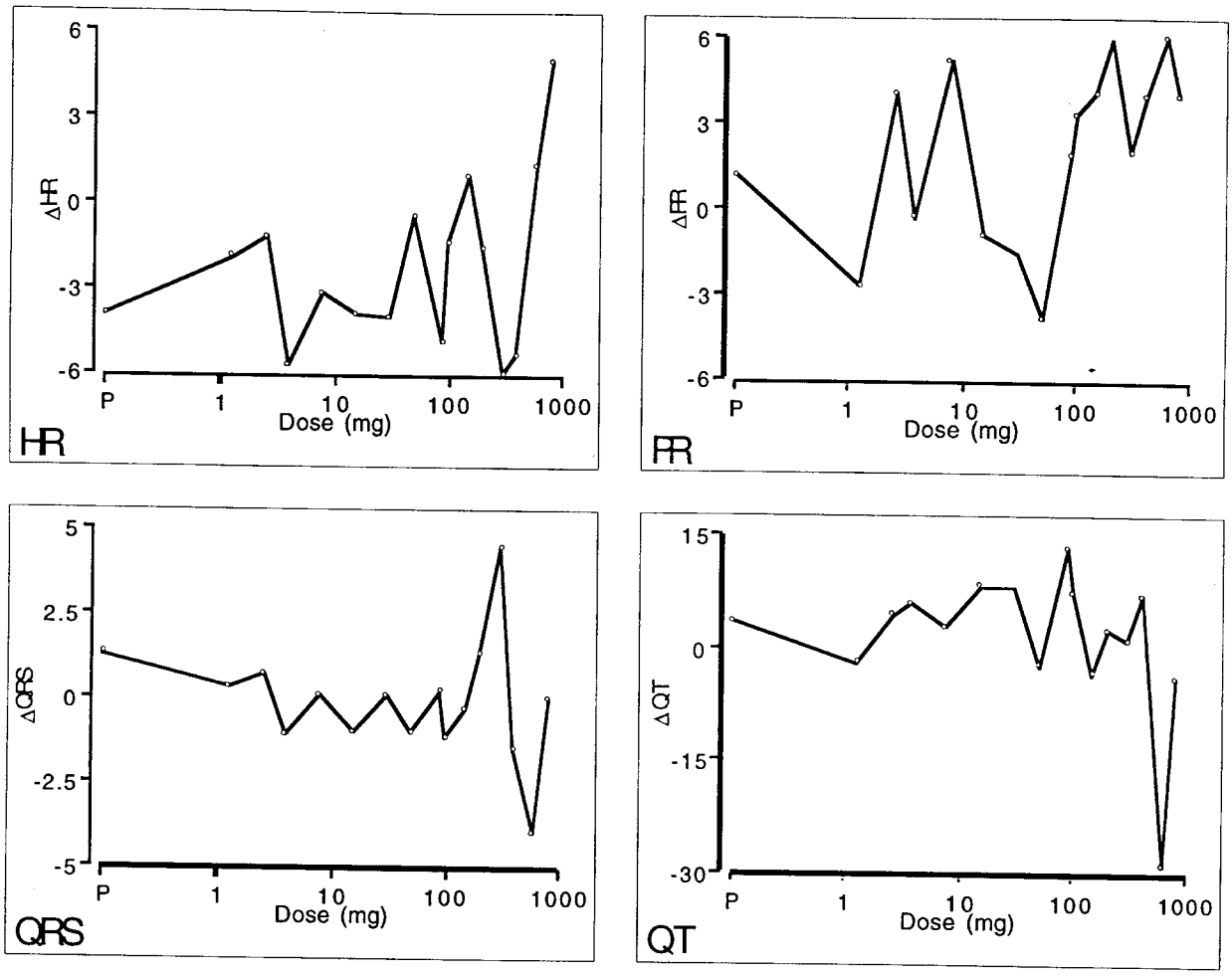

Figure 6. ECG data (Studies 148-001, -004, -201, and -201A.

8.2.5. Pharmacologic basis for safety issues

Sildenafil is a selective inhibitor of phosphodiesterase, an enzyme that catalyzes the cleavage of cAMP or cGMP. Different tissues have different forms of this enzyme, and these different forms have different affinities for sildenafil.

Sildenafil has the lowest IC_{50} for PDE5—about 3 nM. PDE5 is found in the corpus cavernosum, platelets, skeletal muscle, and vascular and visceral smooth muscle. The IC_{50} for PDE6, found in the retina, is about 30 nM. The IC50 for other phosphodiesterases is 7 μM (skeletal muscle PDE4) to 68 μM (corpus cavernosum PDE2), with cardiac muscle PDE3 (involved in the action of milrinone and other inotropes) somewhere in between. Thus, sildenafil has a high degree of selectivity (~1000-fold) for PDE5 and PDE6.

The role of phosphodiesterase is illustrated (for vascular smooth muscle) in Figure 7 below. Endothelial receptors mediate activity of nitric oxide synthase. NO diffuses from endothelial cells (or comes from organic NO donors like glyceryl trinitrate) to smooth muscle cells where it activates guanylate cyclase. Guanylate cyclase catalyzes the formation of cGMP from GTP. Cyclic GMP is, in turn, broken to GMP by the action of phosphodiesterase. An increase in cGMP, resulting from inhibition of phosphodiesterase, causes a reduction in intracellular calcium, and that leads to relaxation of the smooth muscle cells. Similar mechanisms of control of intracellular calcium probably mediate actions of this system in other cells.
On the basis of the proposed mechanism of action, relative affinities of sildenafil for different forms of phosphodiesterase, and the distribution of phosphodiesterase in

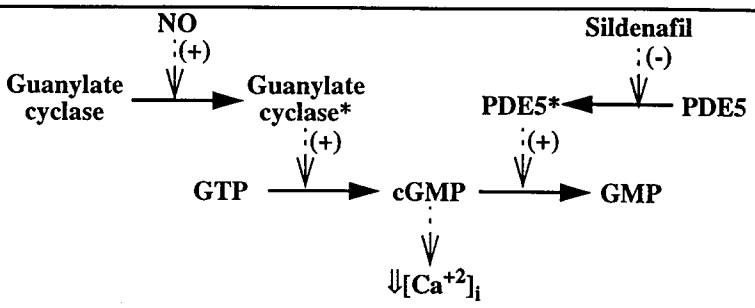

Figure 7. Presumed pharmacological basis for actions of sildenafil.

different tissues, there are effects of sildenafil that can be predicted. These effects include (a) penile erection resulting from relaxation of smooth muscle controlling inflow of blood to the corpus cavernosum, (b) systemic vasodilation and, possibly, hypotension, (c) inhibition of platelet aggregation and increased risk of hemorrhage, (d) skeletal muscle weakness, (e) reduced activity of the gastrointestinal tract, and (f) interference with vision. Each of the potential safety concerns is considered separately.

8.2.5.1. Vital signs

As shown in Study 148-204[7], sildenafil produces peripheral vasodilation, and in phase III studies, where vital signs were not recorded in close association with dosing, sildenafil was associated with vasodilation as an adverse event more commonly than was placebo. Study 148-301[8] was a study of acute hemodynamics of intravenous sildenafil in subjects with chronic ischemic heart disease (not erectile dysfunction). There, sildenafil administration was associated with a blood pressure reduction from baseline of 12/11 mmHg, accompanied by a 10% increase in heart rate[9]. Study of sildenafil (25 mg tid) with glyceryl trinitrate[10] showed a baseline- and placebo-subtracted effect on blood pressure attributable to sildenafil of -15/-5 mmHg with little effect on heart rate. Study of sildenafil (single 100-mg dose) and amlodipine[11] produced peak placebo- and baseline-subtracted effects on blood pressure of -8/-6 mmHg supine and -11/-9 mmHg standing, again with little effect on heart rate.

Sildenafil doses of 800 mg were associated with transient, potentially clinically significant reductions in blood pressure and increases in heart rate in normal male volunteers, as shown in Study 148-004[12]. There was one case of syncope in this study. Available data are not adequate to establish the full dose-response relationship for the effects of sildenafil on blood pressure; hypotension may be the most serious potential adverse effect associated with overdosage.

Sildenafil was otherwise uncommonly associated with symptoms of orthostatic hypotension or with syncope.

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7. *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.* on page 133.
8. *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.* on page 181.
9. It was also accompanied by a 20% reduction in cardiac output. Systemic vascular resistance was not calculated, but, by implication, it must have increased. Most likely the cardiac output values are in error, since there is other evidence of systemic vasodilation.
10. *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.* on page 141.
11. *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.
12. *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.

8.2.5.2. Hemorrhage

The sponsor undertook several clinical trials pertinent to assessing the risk of hemorrhage with sildenafil. Bleeding time and platelet aggregation[13] in response to ADP was assessed in Study 148-206[14], 2, 8, and 12 hours after placebo or sildenafil 50 mg. There was no effect bleeding time and no direct effect of sildenafil on platelet aggregation. However, sildenafil produced a 10-fold decrease in the IC_{50} for sodium nitroprusside.

8.2.5.3. Weakness

Weakness was not formally assessed in the clinical development program (and perhaps it is not true that inhibition of PDE5 lowers intracellular calcium in skeletal muscle or that lowering intracellular calcium leads to weakness. Weakness was reported as an adverse event by fewer than 1% of subjects on sildenafil.

8.2.5.4. Decreased gastrointestinal motility

Gastrointestinal motility was not formally assessed in the clinical development program (and perhaps it is not true that inhibition of PDE5 lowers intracellular calcium in visceral muscle or that lowering intracellular calcium leads to decreased motility. Gastrointestinal symptoms were more commonly reported on sildenafil (14%) than on placebo (6.6%) in studies with flexible-dosing schedules. Specific symptoms more common on sildenafil than on placebo included dyspepsia (6.5 vs. 1.7%), diarrhea (2.0 vs 1.0%), nausea (1.2 vs. 0.4%), and tooth disorder (1.1 vs. 0.8%), none of which are easy to associate with the pharmacological mechanism.

8.2.5.5. Vision abnormalities

Because of novel adverse events pertaining to abnormalities in vision, the sponsor performed 2 studies with a battery of tests of visual acuity, contrast sensitivity, color discrimination, pupillometry, electroretinography, photostress, and visual fields. Study 148-223[15] was a single-dose crossover study with doses 50, 100, and 200 mg, and placebo. Study 148-232[16] was a crossover study of placebo and sildenafil 200 mg. These studies demonstrated a dose-related effect of sildenafil on color discrimination, probably restricted to the blue-green part of the spectrum. The effect was manifest particularly 1 to 2 hours after dosing, around the time of the peak plasma levels. Electroretinograms demonstrated a reduced amplitude response to blue light coincident with the color discrimination impairment and presumably a manifestation of the same defect. Study 232 included a cohort of subjects with diabetic retinopathy, but these results were not reported with the NDA.

The clinical significance of effects on vision cannot be unambiguously determined from these data. The effects appear to be short-lived and without collateral effects on aspects of vision which might lead to accidents.

8.3. Summary of key safety findings

- The safety data collected with the sildenafil development program was adequate in terms of doses studied, dosage schedules, duration of exposure, total number of subjects exposed, and special studies performed, to allow the usual level of confidence in an assessment of the risks of sildenafil for its proposed indication.
- There was one death, a suicide, on placebo. There were 8 deaths on sildenafil or within 30 days of treatment. There were 2 deaths of non-cardiovascular causes: One was a metastatic bladder carcinoma—in which a role of study drug is not plausible. The other was a death associated with a fall, cerebral hemorrhage, and pulmonary sepsis, in a subject with pre-existing arrhythmia; a role of study

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13. Platelets can be induced to aggregate in vitro with ADP. ADP-mediated platelet aggregation can be inhibited in a dose-related manner by the nitric-oxide donor sodium nitroprusside. The effect of sildenafil was assessed by the effect on the dose-response curve for sodium nitroprusside.
14. *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.* on page 134
15. *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.* on page 160.
16. *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.

drug cannot be excluded. Four subjects died from myocardial infarctions, 3 of whom had pertinent histories or evident risk factors. One was a post-operative death in a subject with pre-existing heart failure, and one was a peri-operative death in a study of chronic stable angina. Thus, a small number of deaths might represent increased cardiovascular risk associated with sildenafil.

- Increased cardiovascular risk was not apparent from withdrawals from studies for arrhythmias or myocardial infarctions—despite smaller numbers of subjects and lower periods of exposure, there were more such withdrawals on placebo. Nor was risk evident in comparisons of overall cardiovascular event rates, ECG data, or vital signs.
- Rates of withdrawal from placebo-controlled studies were lower for subjects randomized to sildenafil than for subjects randomized to placebo, with most of the difference attributable to withdrawals for lack of effectiveness. Rates of withdrawal for adverse events were similar on placebo and sildenafil.
- Rates of withdrawal from open-label extensions were quite low—about 10%, with lack of effectiveness being the most common cause.
- The most common adverse event resulting in withdrawal was headache, and this was much more common on sildenafil than on placebo. Adverse events were an uncommon cause for withdrawal from open-label extensions, but among such withdrawals, headache was not uncommon.
- Adverse events reported 'significantly' more commonly on sildenafil than on placebo included headache, vasodilation, dyspepsia, and visual disturbances. All of these can plausibly be linked to pharmacological properties of sildenafil. For the most part, they appear to be dose-related.
- Careful study of blood pressure in the setting of another blood pressure-lowering agent—nitroglycerin or amlodipine—reveals a potentially clinically significant further reduction of blood pressure caused by sildenafil. This effect develops and declines with a time course of hours, similar to the time course of plasma levels of sildenafil after a dose. Although this effect was not associated with symptomatology in trials that included subjects on antihypertensive agents, it remains a safety concern.
- Other adverse events bearing apparent relationship to sildenafil—headaches, dyspepsia, vasodilation, and vision abnormalities—appear to be nuisances of short duration, sufficient to be dose-limiting, but they are not safety concerns. In particular, the vision disturbance has been fairly well characterized, and it does not appear to pose a risk to men operating motor vehicles or other heavy equipment.
- A few effects of sildenafil were expected on the basis of the distribution of phosphodiesterase or observed effects in animals but were missing from the safety experience. Phosphodiesterase inhibition in visceral smooth muscle predictably produced lower gastrointestinal motility in animals, but was without obvious symptomatology, except, perhaps, dyspepsia, in man. Phosphodiesterase inhibition in platelets did not appear to increase the risk of hemorrhage in man or animals.