

Center for Drug Evaluation and Research

Table of Contents

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Table of contents

Section 1. Materials utilized in review.....1
 Section 1.1. Materials from NDA/IND1
 Section 1.2. Related reviews or consults1
 Section 1.3. Other resources1
 Section 2. Background2
 Section 2.1. Indication.....2
 Section 2.2. Information from related pharmacologically related agents.....2
 Section 2.3. Administrative history.....2
 Section 2.4. Proposed labeling.....2
 Section 2.5. Foreign marketing2
 Section 2.6. Other background information2
 Section 3. Chemistry, manufacturing, and controls3
 Section 3.1. Basis of review.....3
 Section 3.2. Structure3
 Section 3.3. Deficiencies3
 Section 4. Animal pharmacology4
 Section 4.1. Basis of review.....4
 Section 4.2. Mechanism of action.....4
 Section 4.2.1. Screening for other activities4
 Section 4.3. Pharmacokinetics.....5
 Section 4.4. Toxicology.....5
 Section 4.4.1. Genetic toxicity5
 Section 4.4.2. Single-dose5
 Section 4.4.3. Sub-chronic/chronic.....5
 Section 4.4.3.1. Oral.....5
 Section 4.4.3.1.1. Rats5
 Section 4.4.3.1.2. Dogs6
 Section 4.4.3.1.3. Mice6
 Section 4.4.3.2. Intravenous6
 Section 4.4.3.2.1. Rats6
 Section 4.4.3.2.2. Dogs6
 Section 4.4.4. Chronic.....6
 Section 4.4.4.1. Rats6
 Section 4.4.4.2. Mice6
 Section 4.4.5. Special toxicity studies.....6
 Section 4.4.6. Safety margin6
 Section 4.5. Summary of significant findings.....7
 Section 5. Description of clinical data sources.....8
 Section 5.1. Primary source data8

Section 5.1.1. Study type and design and subject enumeration	8
Section 5.1.1.1. Controlled studies	8
Section 5.1.1.2. Clinical pharmacology	9
Section 5.1.1.3. Open-label extensions	11
Section 5.1.1.4. Studies not reviewed in detail	12
Section 5.1.2. Enumeration	13
Section 5.1.3. Demographics	13
Section 5.1.4. Extent of exposure	14
Section 5.1.4.1. Placebo-controlled experience	14
Section 5.1.4.2. Open-label experience	15
Section 5.1.4.3. Safety updates	15
Section 5.2. Secondary source data	15
Section 5.2.1. Other studies	15
Section 5.2.2. Post-marketing experience	15
Section 5.2.3. Literature	15
Section 5.3. Adequacy of clinical experience	15
Section 5.4. Data quality and completeness	15
Section 6. Clinical pharmacology and biopharmaceutics	16
Section 6.1. Bioavailability/bioequivalence	16
Section 6.1.1. Absolute bioavailability	16
Section 6.1.2. Food effects	16
Section 6.1.3. Bioequivalence	16
Section 6.2. Pharmacokinetics	16
Section 6.2.1. Single-dose pharmacokinetics	16
Section 6.2.2. Multiple-dose pharmacokinetics	17
Section 6.2.3. ADME	17
Section 6.2.4. Plasma level-dose relationship	18
Section 6.2.5. Concentrations in semen	18
Section 6.2.6. Protein binding	18
Section 6.3. Special populations	19
Section 6.3.1. Renal impairment	19
Section 6.3.2. Hepatic impairment	19
Section 6.3.3. Age	19
Section 6.3.4. Diabetes	20
Section 6.3.5. Erectile dysfunction	20
Section 6.4. Drug interactions	20
Section 6.4.1. Tolbutamide	20
Section 6.4.2. Warfarin	20
Section 6.4.3. Ethanol	20
Section 6.4.4. Calcium channel blockers	20
Section 6.4.5. Cimetidine	20
Section 6.4.6. Maalox	20
Section 6.4.7. Erythromycin	20
Section 6.4.8. CYP3A4 inducers	21
Section 6.4.9. Diuretics	21
Section 6.4.10. β -blockers	21
Section 6.4.11. CYP2C9 inhibitors	21
Section 6.4.12. CYP2D6 inhibitors	21
Section 6.4.13. ACE inhibitors and angiotensin II antagonists	21

Section 6.4.14. Inhibition of CYP by sildenafil and UK-103,320	21
Section 6.5. Population pharmacokinetic analysis	21
Section 6.6. Pharmacokinetic/pharmacodynamic relationships	21
Section 6.7. Formulations	22
Section 6.8. Dissolution	22
Section 6.9. Assay	24
Section 6.10. Comments	24
Section 6.11. Recommendation	24
Section 7. Integrated review of effectiveness	25
Section 7.1. Mechanism of action	25
Section 7.1.1. Single-dose studies	25
Section 7.1.1.1. Mixed etiology	25
Section 7.1.1.2. Psychogenic etiology	25
Section 7.1.1.3. Diabetes	26
Section 7.1.1.4. Spinal cord injury	26
Section 7.1.2. Multiple-dose studies	26
Section 7.1.2.1. Psychogenic etiology	26
Section 7.1.3. Effects by etiology of erectile dysfunction	26
Section 7.1.4. Time course of effects after a dose	26
Section 7.1.5. Time course of effects with repetitive dosing	26
Section 7.1.6. Relationship between dose and erectile function	26
Section 7.1.7. Relationship between plasma levels and erectile function	27
Section 7.2. Effects on sexual performance	27
Section 7.2.1. Methods of assessment	27
Section 7.2.1.1. Primary	27
Section 7.2.1.2. Supportive	27
Section 7.2.2. Dose dependence	27
Section 7.2.2.1. Common characteristics of fixed-dose studies	27
Section 7.2.2.2. Fixed-dose studies assessed by IIEF	28
Section 7.2.2.2.1. Analyses of sexual performance by IIEF	28
Section 7.2.2.2.2. Analyses of other IIEF questions	30
Section 7.2.2.2.3. Analyses of event logs	31
Section 7.2.3. Titration studies	32
Section 7.2.3.1. Common characteristics of titration studies	32
Section 7.2.3.2. Titration studies assessed by IIEF	32
Section 7.2.3.2.1. Analyses of sexual performance by IIEF	33
Section 7.2.3.2.2. Analyses of other IIEF questions	34
Section 7.2.3.2.3. Analyses of event logs	35
Section 7.3. Summary of key effectiveness findings	36
Section 7.3.1. Mechanism of action	36
Section 7.3.2. Dose-dependent effects	36
Section 7.3.3. Time course of effects	36
Section 7.3.3.1. Time course after a dose	36
Section 7.3.3.2. Time course with repeated dosing	37
Section 7.3.4. Effectiveness in sub-groups	37
Section 7.3.4.1. Non-specific organic etiology	37
Section 7.3.4.2. Psychogenic etiology	37
Section 7.3.4.3. Diabetes	38

Section 7.3.4.4. Spinal cord trauma	38
Section 7.3.4.5. Blacks	39
Section 7.3.4.6. Elderly	39
Section 8. Integrated review of safety.....	40
Section 8.1. Methodology	40
Section 8.1.1. Deaths.....	40
Section 8.1.2. Serious adverse events	40
Section 8.1.3. Withdrawals and other significant adverse events	40
Section 8.1.3.1. Overall profile of withdrawals	40
Section 8.1.3.2. Adverse events associated with withdrawal.....	40
Section 8.1.3.3. Other significant adverse events	40
Section 8.1.4. Other search strategies	40
Section 8.1.5. Adverse event incidence	40
Section 8.1.5.1. Approach to eliciting adverse events in the development program	40
Section 8.1.5.2. Appropriateness of adverse event categorization and preferred terms.....	40
Section 8.1.5.3. Identifying common and drug-related adverse events	40
Section 8.1.5.4. Additional analyses	40
Section 8.1.6. Laboratory findings	40
Section 8.1.6.1. Extent of laboratory testing	40
Section 8.1.6.2. Selection of studies and analyses for drug-control comparisons	40
Section 8.1.6.3. Standard analyses	41
Section 8.1.6.3.1. Analyses focussed on central tendency and outliers	41
Section 8.1.6.3.2. Withdrawals for laboratory abnormalities.....	41
Section 8.1.7. Vital signs.....	41
Section 8.1.8. ECGs	41
Section 8.1.9. Special studies.....	41
Section 8.1.10. Withdrawal phenomena	41
Section 8.1.11. Abuse potential.....	41
Section 8.1.12. Human reproduction data.....	41
Section 8.1.13. Overdose experience	41
Section 8.2. Safety results	41
Section 8.2.1. Deaths.....	41
Section 8.2.2. Withdrawals	42
Section 8.2.2.1. Withdrawals for any cause.....	42
Section 8.2.2.1.1. Withdrawals from placebo-controlled studies.....	42
Section 8.2.2.1.2. Withdrawals from open-label extensions.....	43
Section 8.2.2.2. Withdrawals for adverse events.....	43
Section 8.2.2.2.1. Withdrawals from placebo-controlled studies.....	43
Section 8.2.2.2.2. Withdrawals from open-label extensions.....	47
Section 8.2.3. Common adverse events	48
Section 8.2.3.1. Relationship to dose	48
Section 8.2.3.2. Overall incidence.....	49
Section 8.2.4. Laboratory data	50
Section 8.2.4.1. Hepatic function	50
Section 8.2.4.2. Renal function	50
Section 8.2.4.3. Electrolytes, hematology, etc.....	50
Section 8.2.4.4. Vital signs.....	51
Section 8.2.4.5. ECG	52
Section 8.2.5. Pharmacologic basis for safety issues.....	53
Section 8.2.5.1. Vital signs.....	54
Section 8.2.5.2. Hemorrhage.....	55
Section 8.2.5.3. Weakness.....	55

Section 8.2.5.4. Decreased gastrointestinal motility	55
Section 8.2.5.5. Vision abnormalities	55
Section 8.3. Summary of key safety findings	55
Section 9. Labeling review	57
Section 10. Summary and recommendations	69
Section 10.1. Chemistry	69
Section 10.2. Pharmacology and toxicology	69
Section 10.3. Biopharmaceutics	69
Section 10.4. Effectiveness	69
Section 10.5. Safety	69
Section 10.6. Recommendation	70
Section 10.7. Comments on label	70
Appendix A. Study reports	71
Appendix A1. In vitro metabolism studies	71
Appendix A1.1. Report DM2: In vitro metabolism of UK-92480 in hepatic microsomes from rat, dog, rabbit, and man	71
Appendix A1.1.1. Methods	71
Appendix A1.1.2. Results	71
Appendix A1.2. Report DM3: In vitro metabolism of UK-92480 in human liver microsomes enzymology of UK-103,320 formation.	71
Appendix A1.2.1. Source documents	71
Appendix A1.2.2. Objectives	71
Appendix A1.2.3. Methods	71
Appendix A1.2.4. Results	72
Appendix A1.2.5. Conclusion	73
Appendix A1.3. Report DM4: In vitro inhibition studies on UK-92480 in human liver microsomes.	73
Appendix A1.3.1. Source documents	73
Appendix A1.3.2. Objectives	73
Appendix A1.3.3. Results	73
Appendix A1.3.4. Conclusion	73
Appendix A1.4. Report DM5: In vitro metabolism and P450 inhibition studies of UK-103,320 in human liver microsomes.	73
Appendix A1.4.1. Source documents	73
Appendix A1.4.2. Objectives	73
Appendix A1.4.3. Methods	74
Appendix A1.4.4. Results	74
Appendix A1.5. Report DM34: In vitro interaction between UK-92480 and the CYP3A4 substrates terfenadine and testosterone in human liver microsomes.	74
Appendix A1.5.1. Source documents	74
Appendix A1.5.2. Objectives	74
Appendix A1.5.3. Results	74
Appendix A2. Population pharmacokinetic and pharmacodynamic analysis of sildenafil phase III data	75

Appendix A2.1. Methods	75
Appendix A2.1.1. Data collection	75
Appendix A2.1.2. Pharmacokinetic modeling.....	75
Appendix A2.1.3. Pharmacokinetic-pharmacodynamic modeling	75
Appendix A2.2. Results.....	76
Appendix A2.2.1. Sildenafil pharmacokinetics.....	77
Appendix A2.2.2. UK-103,320 pharmacokinetics.....	79
Appendix A2.2.3. Pharmacodynamics.....	81
Appendix A2.2.4. Adverse events.....	84
Appendix A2.3. Summary	85
Appendix A3. Development and validation of the primary efficacy instrument (International Index of Erectile Function; IIEF).	87
Appendix A3.1. Source documents	87
Appendix A3.2. IIEF development	87
Appendix A3.3. IIEF validation studies	87
Appendix A4. Study 148-001: Phase I single dose, open study of the clinical pharmacology of sildenafil in elderly and young healthy male volunteers.	89
Appendix A4.1. Source documents	89
Appendix A4.2. Investigators	89
Appendix A4.3. Study dates	89
Appendix A4.4. Study design	89
Appendix A4.4.1. Objectives	89
Appendix A4.4.2. Formulation	89
Appendix A4.4.3. Population.....	89
Appendix A4.4.4. Procedures	89
Appendix A4.4.5. Assay	89
Appendix A4.4.6. Analysis	89
Appendix A4.4.7. Safety.....	89
Appendix A4.5. Results.....	89
Appendix A4.5.1. Conduct.....	89
Appendix A4.5.2. Pharmacokinetics.....	89
Appendix A4.5.3. Safety.....	91
Appendix A4.6. Summary	91
Appendix A5. 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.	92
Appendix A5.1. Source documents	92
Appendix A5.2. Investigators	92
Appendix A5.3. Study dates	92
Appendix A5.4. Study design	92
Appendix A5.5. Results.....	93
Appendix A5.5.1. Conduct.....	93
Appendix A5.5.2. Pharmacokinetics.....	93
Appendix A5.5.3. Safety.....	93

Appendix A5.6. Summary	93
Appendix A6. 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.....	94
Appendix A6.1. Source documents	94
Appendix A6.2. Investigators	94
Appendix A6.3. Study dates	94
Appendix A6.4. Study design	94
Appendix A6.5. Results	94
Appendix A6.5.1. Conduct.....	94
Appendix A6.5.2. Pharmacokinetics.....	95
Appendix A6.5.3. Safety.....	95
Appendix A6.6. Summary	95
Appendix A7. 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.....	96
Appendix A7.1. Source documents	96
Appendix A7.2. Investigators	96
Appendix A7.3. Study dates	96
Appendix A7.4. Study design	96
Appendix A7.5. Results	96
Appendix A7.5.1. Conduct.....	96
Appendix A7.5.2. Pharmacokinetics.....	96
Appendix A7.5.3. Safety.....	98
Appendix A7.6. Summary	98
Appendix A8. 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.....	99
Appendix A8.1. Source documents	99
Appendix A8.2. Investigators	99
Appendix A8.3. Study dates	99
Appendix A8.4. Study design	99
Appendix A8.5. Results.....	100
Appendix A8.5.1. Conduct.....	100
Appendix A8.5.2. Effectiveness	100
Appendix A8.5.3. Safety.....	101
Appendix A8.6. Summary	101
Appendix A9. Study 148-101C: An open, non-comparative study to assess the long-term safety of sildenafil in patients with erectile dysfunction.	102
Appendix A9.1. Source documents	102
Appendix A9.2. Investigators	102

Appendix A9.3. Study dates	102
Appendix A9.4. Study design	102
Appendix A9.5. Results.....	102
Appendix A9.5.1. Conduct.....	102
Appendix A9.5.2. Effectiveness	103
Appendix A9.5.3. Safety.....	103
Appendix A9.6. Summary	103
Appendix A10. 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.....	104
Appendix A10.1. Source documents	104
Appendix A10.2. Investigators	104
Appendix A10.3. Study dates	104
Appendix A10.4. Study design	104
Appendix A10.5. Results.....	105
Appendix A10.5.1. Conduct.....	105
Appendix A10.5.2. Effectiveness	107
Appendix A10.5.3. Safety.....	110
Appendix A10.5.4. Long-term.....	110
Appendix A10.6. Summary	110
Appendix A11. 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.	111
Appendix A11.1. Source documents	111
Appendix A11.2. Investigators	111
Appendix A11.3. Study dates	111
Appendix A11.4. Study design	111
Appendix A11.5. Results.....	112
Appendix A11.5.1. Conduct.....	112
Appendix A11.5.2. Effectiveness	114
Appendix A11.5.3. Safety.....	116
Appendix A11.5.4. Long-term.....	116
Appendix A11.6. Summary	117
Appendix A12. 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.....	118
Appendix A12.1. Source documents	118
Appendix A12.2. Investigators	118
Appendix A12.3. Study dates	118
Appendix A12.4. Study design	118
Appendix A12.5. Results.....	119

Appendix A12.5.1. Conduct.....	119
Appendix A12.5.2. Effectiveness	121
Appendix A12.5.3. Safety.....	122
Appendix A12.5.4. Long-term.....	122
Appendix A12.6. Summary	123
Appendix A13. 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.....	124
Appendix A13.1. Source documents	124
Appendix A13.2. Investigators	124
Appendix A13.3. Study dates	124
Appendix A13.4. Study design	124
Appendix A13.5. Results.....	124
Appendix A13.5.1. Conduct.....	124
Appendix A13.5.2. Effectiveness	125
Appendix A13.5.3. Pharmacokinetics.....	125
Appendix A13.5.4. Safety.....	125
Appendix A13.6. Summary	125
Appendix A14. 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.....	126
Appendix A14.1. Source documents	126
Appendix A14.2. Investigators	126
Appendix A14.3. Study dates	126
Appendix A14.4. Study design	126
Appendix A14.5. Results.....	127
Appendix A14.5.1. Conduct.....	127
Appendix A14.5.2. Effectiveness	128
Appendix A14.5.3. Safety.....	130
Appendix A14.6. Summary	130
Appendix A15. 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.....	131
Appendix A15.1. Source documents	131
Appendix A15.2. Investigators	131
Appendix A15.3. Study dates	131
Appendix A15.4. Study design	131
Appendix A15.4.1. Objectives	131
Appendix A15.4.2. Formulation.....	131
Appendix A15.4.3. Population.....	131
Appendix A15.4.4. Procedures	131
Appendix A15.4.5. Assay	131

Appendix A15.4.6. Analysis.....	131
Appendix A15.4.7. Safety.....	131
Appendix A15.5. Results.....	131
Appendix A15.5.1. Pharmacokinetics.....	131
Appendix A15.6. Summary	132
Appendix A16. 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.....	133
Appendix A16.1. Source documents	133
Appendix A16.2. Investigators	133
Appendix A16.3. Study dates	133
Appendix A16.4. Study design	133
Appendix A16.5. Results.....	133
Appendix A16.5.1. Conduct.....	133
Appendix A16.5.2. Pharmacokinetics.....	133
Appendix A16.5.3. Pharmacodynamics.....	133
Appendix A16.5.4. Safety.....	133
Appendix A16.6. Summary	133
Appendix A17. 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.....	134
Appendix A17.1. Source documents	134
Appendix A17.2. Investigators	134
Appendix A17.3. Study dates	134
Appendix A17.4. Study design	134
Appendix A17.5. Results.....	134
Appendix A17.5.1. Conduct.....	134
Appendix A17.5.2. Pharmacokinetics.....	134
Appendix A17.5.3. Pharmacodynamics.....	134
Appendix A17.5.4. Safety.....	134
Appendix A17.6. Summary	134
Appendix A18. 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.	135
Appendix A18.1. Source documents	135
Appendix A18.2. Investigators	135
Appendix A18.3. Study dates	135
Appendix A18.4. Study design	135
Appendix A18.4.1. Objectives	135
Appendix A18.4.2. Formulation.....	135
Appendix A18.4.3. Population.....	135
Appendix A18.4.4. Procedures.....	135
Appendix A18.4.5. Assay	135
Appendix A18.4.6. Analysis.....	135

Appendix A18.4.7. Safety.....	136
Appendix A18.5. Results.....	136
Appendix A18.5.1. Conduct.....	136
Appendix A18.5.2. Pharmacokinetics.....	136
Appendix A18.5.3. Pharmacodynamics.....	137
Appendix A18.5.4. Safety.....	137
Appendix A18.6. Summary	137
Appendix A19. 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.	139
Appendix A19.1. Source documents	139
Appendix A19.2. Investigators	139
Appendix A19.3. Study dates	139
Appendix A19.4. Study design	139
Appendix A19.4.1. Objectives	139
Appendix A19.4.2. Formulation.....	139
Appendix A19.4.3. Population.....	139
Appendix A19.4.4. Procedures	139
Appendix A19.4.5. Assay	139
Appendix A19.4.6. Analysis.....	139
Appendix A19.4.7. Safety.....	139
Appendix A19.5. Results.....	139
Appendix A19.5.1. Pharmacokinetics.....	139
Appendix A19.6. Summary	140
Appendix A20. 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.....	141
Appendix A20.1. Source documents	141
Appendix A20.2. Investigators	141
Appendix A20.3. Study dates	141
Appendix A20.4. Study design	141
Appendix A20.5. Results.....	141
Appendix A20.5.1. Conduct.....	141
Appendix A20.5.2. Pharmacokinetics.....	141
Appendix A20.5.3. Pharmacodynamics.....	141
Appendix A20.5.4. Safety.....	141
Appendix A20.6. Summary	141
Appendix A21. 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.	142
Appendix A21.1. Source documents	142
Appendix A21.2. Investigators	142
Appendix A21.3. Study dates	142
Appendix A21.4. Study design	142

Appendix A21.4.1. Objectives	142
Appendix A21.4.2. Formulation.....	142
Appendix A21.4.3. Population.....	142
Appendix A21.4.4. Procedures	142
Appendix A21.4.5. Assay	142
Appendix A21.4.6. Analysis	142
Appendix A21.4.7. Safety.....	142
Appendix A21.5. Results.....	142
Appendix A21.5.1. Pharmacokinetics.....	142
Appendix A21.5.2. Safety.....	144
Appendix A21.6. Summary	144
Appendix A22. 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 [¹⁴ C]-UK-92,480.....	145
Appendix A22.1. Source documents	145
Appendix A22.2. Investigators	145
Appendix A22.3. Study dates	145
Appendix A22.4. Study design	145
Appendix A22.4.1. Objectives	145
Appendix A22.4.2. Formulation.....	145
Appendix A22.4.3. Population.....	145
Appendix A22.4.4. Procedures	145
Appendix A22.4.5. Assay	145
Appendix A22.4.6. Analysis	146
Appendix A22.4.7. Safety.....	146
Appendix A22.5. Results.....	146
Appendix A22.5.1. Pharmacokinetics.....	146
Appendix A22.6. Summary	149
Appendix A23. 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.....	150
Appendix A23.1. Source documents	150
Appendix A23.2. Investigators	150
Appendix A23.3. Study dates	150
Appendix A23.4. Study design	150
Appendix A23.5. Results.....	150
Appendix A23.5.1. Conduct.....	150
Appendix A23.5.2. Pharmacodynamics.....	150
Appendix A23.5.3. Safety.....	150
Appendix A23.6. Summary	150
Appendix A24. 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.....	151

Appendix A24.1. Source documents	151
Appendix A24.2. Investigators	151
Appendix A24.3. Study dates	151
Appendix A24.4. Study design	151
Appendix A24.4.1. Objectives	151
Appendix A24.4.2. Formulation	151
Appendix A24.4.3. Population	151
Appendix A24.4.4. Procedures	151
Appendix A24.4.5. Assay	151
Appendix A24.4.6. Analysis	151
Appendix A24.4.7. Safety	151
Appendix A24.5. Results	151
Appendix A24.5.1. Pharmacokinetics	151
Appendix A24.5.2. Safety	152
Appendix A24.6. Summary	152
Appendix A25. 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.	153
Appendix A25.1. Source documents	153
Appendix A25.2. Investigators	153
Appendix A25.3. Study dates	153
Appendix A25.4. Study design	153
Appendix A25.4.1. Objectives	153
Appendix A25.4.2. Formulation	153
Appendix A25.4.3. Population	153
Appendix A25.4.4. Procedures	153
Appendix A25.4.5. Assay	153
Appendix A25.4.6. Analysis	153
Appendix A25.4.7. Safety	153
Appendix A25.5. Results	153
Appendix A25.5.1. Conduct	153
Appendix A25.5.2. Pharmacokinetics	154
Appendix A25.5.3. Safety	154
Appendix A25.6. Summary	154
Appendix A26. 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.	155
Appendix A26.1. Source documents	155
Appendix A26.2. Investigators	155
Appendix A26.3. Study dates	155
Appendix A26.4. Study design	155
Appendix A26.4.1. Objectives	155
Appendix A26.4.2. Formulation	155
Appendix A26.4.3. Population	155

Appendix A26.4.4. Procedures	155
Appendix A26.4.5. Assay	155
Appendix A26.4.6. Safety	155
Appendix A26.5. Results	155
Appendix A26.5.1. Conduct.....	155
Appendix A26.5.2. Pharmacodynamics.....	155
Appendix A26.6. Summary	156
Appendix A27. 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.	157
Appendix A27.1. Source documents	157
Appendix A27.2. Investigators	157
Appendix A27.3. Study dates	157
Appendix A27.4. Study design	157
Appendix A27.4.1. Objectives	157
Appendix A27.4.2. Formulation.....	157
Appendix A27.4.3. Population.....	157
Appendix A27.4.4. Procedures	157
Appendix A27.4.5. Assay	157
Appendix A27.4.6. Analysis.....	157
Appendix A27.4.7. Safety.....	157
Appendix A27.5. Results.....	157
Appendix A27.5.1. Pharmacokinetics.....	157
Appendix A27.6. Summary	158
Appendix A28. 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.	159
Appendix A28.1. Source documents	159
Appendix A28.2. Investigators	159
Appendix A28.3. Study dates	159
Appendix A28.4. Study design	159
Appendix A28.5. Results.....	159
Appendix A28.5.1. Conduct.....	159
Appendix A28.5.2. Pharmacokinetics.....	159
Appendix A28.5.3. Pharmacodynamics.....	159
Appendix A28.5.4. Safety.....	159
Appendix A28.6. Summary	159
Appendix A29. 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.	160
Appendix A29.1. Source documents	160
Appendix A29.2. Investigators	160

Appendix A29.3. Study dates	160
Appendix A29.4. Study design	160
Appendix A29.5. Results.....	160
Appendix A29.5.1. Conduct.....	160
Appendix A29.5.2. Pharmacokinetics.....	160
Appendix A29.5.3. Pharmacodynamics.....	160
Appendix A29.5.4. Safety.....	161
Appendix A29.6. Summary	161
Appendix A30. 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.....	162
Appendix A30.1. Source documents	162
Appendix A30.2. Investigators	162
Appendix A30.3. Study dates	162
Appendix A30.4. Study design	162
Appendix A30.5. Results.....	162
Appendix A30.5.1. Conduct.....	162
Appendix A30.5.2. Pharmacokinetics.....	162
Appendix A30.5.3. Pharmacodynamics.....	162
Appendix A30.5.4. Safety.....	162
Appendix A30.6. Summary	162
Appendix A31. 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.	163
Appendix A31.1. Source documents	163
Appendix A31.2. Investigators	163
Appendix A31.3. Study dates	163
Appendix A31.4. Study design	163
Appendix A31.4.1. Objectives	163
Appendix A31.4.2. Formulation.....	163
Appendix A31.4.3. Population.....	163
Appendix A31.4.4. Procedures	163
Appendix A31.4.5. Assay	163
Appendix A31.4.6. Analysis.....	163
Appendix A31.4.7. Safety.....	163
Appendix A31.5. Results.....	163
Appendix A31.5.1. Conduct.....	163
Appendix A31.5.2. Pharmacokinetics.....	163
Appendix A31.5.3. Safety.....	164
Appendix A31.6. Summary	164
Appendix A32. 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.....	165

Appendix A32.1. Source documents165

Appendix A32.2. Investigators165

Appendix A32.3. Study dates165

Appendix A32.4. Study design165

 Appendix A32.4.1. Objectives165

 Appendix A32.4.2. Formulation.....165

 Appendix A32.4.3. Population.....165

 Appendix A32.4.4. Procedures165

 Appendix A32.4.5. Assay165

 Appendix A32.4.6. Analysis.....165

 Appendix A32.4.7. Safety.....165

Appendix A32.5. Results.....165

 Appendix A32.5.1. Conduct.....165

 Appendix A32.5.2. Pharmacokinetics.....165

 Appendix A32.5.3. Safety.....166

Appendix A32.6. Summary166

Appendix A33. 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.....167

 Appendix A33.1. Source documents167

 Appendix A33.2. Investigators167

 Appendix A33.3. Study dates167

 Appendix A33.4. Study design167

 Appendix A33.4.1. Objectives167

 Appendix A33.4.2. Formulation.....167

 Appendix A33.4.3. Population.....167

 Appendix A33.4.4. Procedures167

 Appendix A33.4.5. Assay167

 Appendix A33.4.6. Analysis.....167

 Appendix A33.4.7. Safety.....167

 Appendix A33.5. Results.....167

 Appendix A33.5.1. Conduct.....167

 Appendix A33.5.2. Pharmacokinetics.....167

 Appendix A33.5.3. Safety.....168

 Appendix A33.6. Summary168

Appendix A34. 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.....170

 Appendix A34.1. Source documents170

 Appendix A34.2. Investigators170

 Appendix A34.3. Study dates170

 Appendix A34.4. Study design170

 Appendix A34.4.1. Objectives170

 Appendix A34.4.2. Formulation.....170

 Appendix A34.4.3. Population.....170

Appendix A34.4.4. Procedures	170
Appendix A34.4.5. Assay	170
Appendix A34.4.6. Analysis	170
Appendix A34.5. Results	171
Appendix A34.5.1. Conduct	171
Appendix A34.5.2. Pharmacokinetics	171
Appendix A34.5.3. Pharmacodynamics	172
Appendix A34.5.4. Safety	172
Appendix A34.6. Summary	172
Appendix A35. 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.	173
Appendix A35.1. Source documents	173
Appendix A35.2. Investigators	173
Appendix A35.3. Study dates	173
Appendix A35.4. Study design	173
Appendix A35.5. Results	173
Appendix A35.5.1. Conduct	173
Appendix A35.5.2. Pharmacodynamics	173
Appendix A35.5.3. Safety	174
Appendix A35.6. Summary	174
Appendix A36. 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.	175
Appendix A36.1. Source documents	175
Appendix A36.2. Investigators	175
Appendix A36.3. Study dates	175
Appendix A36.4. Study design	175
Appendix A36.5. Results	175
Appendix A36.5.1. Conduct	175
Appendix A36.5.2. Pharmacodynamics	175
Appendix A36.5.3. Safety	176
Appendix A36.6. Summary	176
Appendix A37. 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.	177
Appendix A37.1. Source documents	177
Appendix A37.2. Investigators	177
Appendix A37.3. Study dates	177
Appendix A37.4. Study design	177

Appendix A37.5. Results.....	177
Appendix A37.5.1. Conduct.....	177
Appendix A37.5.2. Pharmacokinetics.....	177
Appendix A37.5.3. Pharmacodynamics.....	177
Appendix A37.5.4. Safety.....	178
Appendix A37.6. Summary	178
Appendix A38. 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.....	179
Appendix A38.1. Source documents	179
Appendix A38.2. Investigators	179
Appendix A38.3. Study dates	179
Appendix A38.4. Study design	179
Appendix A38.4.1. Objectives	179
Appendix A38.4.2. Formulation.....	179
Appendix A38.4.3. Population.....	179
Appendix A38.4.4. Procedures	179
Appendix A38.4.5. Assay	179
Appendix A38.4.6. Analysis.....	179
Appendix A38.4.7. Safety.....	179
Appendix A38.5. Results.....	179
Appendix A38.5.1. Conduct.....	179
Appendix A38.5.2. Pharmacokinetics.....	179
Appendix A38.5.3. Safety.....	180
Appendix A38.6. Summary	180
Appendix A39. 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.	181
Appendix A39.1. Source documents	181
Appendix A39.2. Investigators	181
Appendix A39.3. Study dates	181
Appendix A39.4. Study design	181
Appendix A39.5. Results.....	181
Appendix A39.5.1. Conduct.....	181
Appendix A39.5.2. Pharmacokinetics.....	181
Appendix A39.5.3. Pharmacodynamics.....	181
Appendix A39.5.4. Safety.....	181
Appendix A39.6. Summary	182
Appendix A40. 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..	183
Appendix A40.1. Source documents	183
Appendix A40.2. Investigators	183
Appendix A40.3. Study dates	183

Appendix A40.4. Study design	183
Appendix A40.5. Results	183
Appendix A40.5.1. Conduct.....	183
Appendix A40.5.2. Pharmacodynamics.....	183
Appendix A40.5.3. Safety.....	183
Appendix A40.6. Summary	183
Appendix A41. 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.	184
Appendix A41.1. Source documents	184
Appendix A41.2. Investigators	184
Appendix A41.3. Study dates	184
Appendix A41.4. Study design	184
Appendix A41.5. Results.....	184
Appendix A41.5.1. Conduct.....	184
Appendix A41.5.2. Pharmacokinetics.....	184
Appendix A41.5.3. Pharmacodynamics.....	184
Appendix A41.5.4. Safety.....	184
Appendix A41.6. Summary	185
Appendix A42. 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.	186
Appendix A42.1. Source documents	186
Appendix A42.2. Investigators	186
Appendix A42.3. Study dates	186
Appendix A42.4. Study design	186
Appendix A42.5. Results.....	186
Appendix A42.5.1. Conduct.....	186
Appendix A42.5.2. Effectiveness	187
Appendix A42.5.3. Safety.....	188
Appendix A42.6. Summary	188
Appendix A43. 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.....	189
Appendix A43.1. Source documents	189
Appendix A43.2. Investigators	189
Appendix A43.3. Study dates	189
Appendix A43.4. Study design	189
Appendix A43.5. Results.....	189
Appendix A43.5.1. Conduct.....	189
Appendix A43.5.2. Effectiveness	190

Appendix A43.5.3. Safety.....	190
Appendix A43.5.4. Long-term.....	190
Appendix A43.6. Summary	190
Appendix A44. 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.	191
Appendix A44.1. Source documents	191
Appendix A44.2. Investigators	191
Appendix A44.3. Study dates	191
Appendix A44.4. Study design	191
Appendix A44.5. Results.....	191
Appendix A44.5.1. Conduct.....	191
Appendix A44.5.2. Effectiveness	192
Appendix A44.5.3. Safety.....	192
Appendix A44.5.4. Long-term.....	192
Appendix A44.6. Summary	192
Appendix A45. 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.	193
Appendix A45.1. Source documents	193
Appendix A45.2. Investigators	193
Appendix A45.3. Study dates	193
Appendix A45.4. Study design	193
Appendix A45.5. Results.....	193
Appendix A45.5.1. Conduct.....	193
Appendix A45.5.2. Effectiveness	194
Appendix A45.5.3. Safety.....	194
Appendix A45.5.4. Long-term.....	194
Appendix A45.6. Summary	194
Appendix A46. 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.	195
Appendix A46.1. Source documents	195
Appendix A46.2. Investigators	195
Appendix A46.3. Study dates	195
Appendix A46.4. Study design	195
Appendix A46.5. Results.....	195
Appendix A46.5.1. Conduct.....	195
Appendix A46.5.2. Effectiveness	195
Appendix A46.5.3. Safety.....	196
Appendix A46.5.4. Long-term.....	196

Appendix A46.6. Summary	196
Appendix A47. 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.	197
Appendix A47.1. Source documents	197
Appendix A47.2. Investigators	197
Appendix A47.3. Study dates	197
Appendix A47.4. Study design	197
Appendix A47.5. Results.....	197
Appendix A47.5.1. Conduct.....	197
Appendix A47.5.2. Effectiveness	198
Appendix A47.5.3. Safety.....	198
Appendix A47.5.4. Long-term.....	198
Appendix A47.6. Summary	198
Appendix A48. 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.	199
Appendix A48.1. Source documents	199
Appendix A48.2. Investigators	199
Appendix A48.3. Study dates	199
Appendix A48.4. Study design	199
Appendix A48.5. Results.....	199
Appendix A48.5.1. Conduct.....	199
Appendix A48.5.2. Effectiveness	200
Appendix A48.5.3. Safety.....	200
Appendix A48.5.4. Long-term.....	200
Appendix A48.6. Summary	200
Appendix A49. 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.	201
Appendix A49.1. Source documents	201
Appendix A49.2. Investigators	201
Appendix A49.3. Study dates	201
Appendix A49.4. Study design	201
Appendix A49.5. Results.....	201
Appendix A49.5.1. Conduct.....	201
Appendix A49.5.2. Pharmacokinetics.....	201
Appendix A49.5.3. Pharmacodynamics.....	201
Appendix A49.5.4. Safety.....	201
Appendix A49.5.5. Long-term.....	202
Appendix A49.6. Summary	202
Appendix A50. 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.203

 Appendix A50.1. Source documents203

 Appendix A50.2. Investigators203

 Appendix A50.3. Study dates203

 Appendix A50.4. Study design203

 Appendix A50.5. Results.....204

 Appendix A50.5.1. Conduct.....204

 Appendix A50.5.2. Effectiveness204

 Appendix A50.5.3. Safety.....205

 Appendix A50.5.4. Long-term.....205

 Appendix A50.6. Summary205

Appendix A51. 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.206

 Appendix A51.1. Source documents206

 Appendix A51.2. Investigators206

 Appendix A51.3. Study dates206

 Appendix A51.4. Study design206

 Appendix A51.5. Results.....207

 Appendix A51.5.1. Conduct.....207

 Appendix A51.5.2. Effectiveness209

 Appendix A51.5.3. Safety.....211

 Appendix A51.5.4. Long-term.....211

 Appendix A51.6. Summary211

Appendix A52. 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.....212

 Appendix A52.1. Source documents212

 Appendix A52.2. Investigators212

 Appendix A52.3. Study dates212

 Appendix A52.4. Study design212

 Appendix A52.5. Results.....213

 Appendix A52.5.1. Conduct.....213

 Appendix A52.5.2. Effectiveness215

 Appendix A52.5.3. Safety.....217

 Appendix A52.6. Summary217

Appendix A53. 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.218

 Appendix A53.1. Source documents218

Appendix A53.2. Investigators	218
Appendix A53.3. Study dates	218
Appendix A53.4. Study design	218
Appendix A53.5. Results.....	219
Appendix A53.5.1. Conduct.....	219
Appendix A53.5.2. Effectiveness	220
Appendix A53.5.3. Safety.....	221
Appendix A53.6. Summary	221
Appendix A54. 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.	222
Appendix A54.1. Source documents	222
Appendix A54.2. Investigators	222
Appendix A54.3. Study dates	222
Appendix A54.4. Study design	222
Appendix A54.5. Results.....	222
Appendix A54.5.1. Conduct.....	222
Appendix A54.5.2. Pharmacokinetics.....	222
Appendix A54.5.3. Pharmacodynamics.....	222
Appendix A54.5.4. Safety.....	222
Appendix A54.6. Summary	222
Appendix A55. 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.....	223
Appendix A55.1. Source documents	223
Appendix A55.2. Investigators	223
Appendix A55.3. Study dates	223
Appendix A55.4. Study design	223
Appendix A55.5. Results.....	223
Appendix A55.5.1. Conduct.....	223
Appendix A55.5.2. Validation	223
Appendix A56. 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.	224
Appendix A56.1. Source documents	224
Appendix A56.2. Investigators	224
Appendix A56.3. Study dates	224
Appendix A56.4. Study design	224
Appendix A56.5. Results.....	224
Appendix A56.5.1. Effectiveness	224
Appendix A56.5.2. Safety.....	224

List of tables

Table 1. Inhibition of phosphodiesterase forms by sildenafil.	4
Table 2. Single-dose pharmacokinetics in mammals.	5
Table 3. Safety factors based upon animal toxicity and human and animal pharmacokinetics.	7
Table 4. Controlled clinical trials of effectiveness.	8
Table 5. Clinical pharmacology trials.	9
Table 6. Long-term, open-label studies.	12
Table 7. Studies not reviewed in detail.	12
Table 8. Subjects exposed in clinical studies.	13
Table 9. Subjects by age in placebo-controlled and open-label studies.	13
Table 10. Etiology of erectile dysfunction in placebo-controlled and open-label studies.	13
Table 11. Baseline disease incidence (%) in placebo-controlled and open-label studies.	14
Table 12. Study drug exposure (doses) in studies 148-102 and 148-361.	14
Table 13. Planned exposure (weeks) in placebo-controlled fixed-dose studies.	14
Table 14. Composition (mg) of sildenafil tablets.	22
Table 15. Fixed-dose studies utilizing the IIEF.	28
Table 16. ITT analyses of IIEF questions 3 and 4 (fixed-dose studies).	29
Table 17. Sub-group analyses of IIEF questions 3 and 4 (Studies 148-102 and 148-364).	29
Table 18. ITT analyses of supportive IIEF questions at week 12 (fixed-dose studies).	30
Table 19. Successful intercourse by event logs (fixed-dose studies).	32
Table 20. Titration studies utilizing the IIEF.	32
Table 21. ITT analyses of IIEF questions 3 and 4 (titration studies).	33
Table 22. Sub-group analyses of IIEF questions 3 and 4 (Studies 148-103 and 148-363).	33
Table 23. ITT analyses of supportive IIEF questions at week 12 (titration studies).	34
Table 24. Successful intercourse by event logs (titration studies).	35
Table 25. Effectiveness in organic erectile dysfunction.	37
Table 26. Effectiveness in psychogenic erectile dysfunction.	37
Table 27. ITT analyses of IIEF questions 3 and 4 (Study 148-104).	38
Table 28. Effectiveness in diabetics with erectile dysfunction.	38
Table 29. Deaths on or within 30 days of study drug.	41
Table 30. Withdrawals from placebo-controlled studies.	42
Table 31. Withdrawals from open-label studies.	43
Table 32. Adverse events leading to withdrawal from placebo-controlled studies.	43
Table 33. Adverse events leading to withdrawal from open-label studies.	47
Table 34. Dose-relatedness of common adverse events in placebo-controlled studies.	49
Table 35. Percentage of subjects with common adverse events in flexible-dosing studies.	49
Table 36. Hepatic function abnormalities in placebo-controlled studies.	50
Table 37. Potentially clinically significant shifts in electrolytes in placebo-controlled studies.	51
Table 38. Potentially clinically significant shifts in hematologic parameters in placebo-controlled studies.	51
Table 39. Relationship between dose at calcium level (Studies 102, 103, 363, and 364).	51
Table 40. Summary of median changes in vital signs in placebo-controlled studies.	52
Table 41. Disappearance half-lives for sildenafil in hepatic microsomes (Report DM2).	71
Table 42. P450 inhibitors (Report DM3).	71
Table 43. UK-103,320 formation in human liver microsomes (Report DM3).	73
Table 44. Correlation between rate of UK-103,320 formation and P450 isoform activity (Report DM3).	73
Table 45. Inhibition of CYP isoforms by sildenafil (Report DM4).	73
Table 46. Inhibition of CYP isoforms by UK-103-320 (Report DM5).	74
Table 47. Pharmacokinetic parameters (mean±SD) for final sildenafil model.	78
Table 48. Effect of addition of covariates to basic sildenafil model (test data).	78
Table 49. Effect of changes in covariates on pharmacokinetic model for sildenafil (final dataset).	79
Table 50. Effect of deletion of studies from final pharmacokinetic model for sildenafil.	79
Table 51. Effect of addition of covariates to basic UK-103,320 model (test data).	79
Table 52. Effect of changes in covariates on pharmacokinetic model for UK-103,320 (final dataset).	81
Table 53. Effect of deletion of studies from final pharmacokinetic model for UK-103,320.	81

Table 54. Effect of additive or proportional E_{max} and estimation method on fit to pharmacodynamic model.	82
Table 55. Effect of deletion of studies from final pharmacodynamic model.	82
Table 56. Estimated D_{50} for question 3, by study.	83
Table 57. Effect of deletion of studies from final pharmacodynamic model.	83
Table 58. Estimated D_{50} for question 4, by study.	84
Table 59. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-001).	91
Table 60. Drug supplies (Study 148-002).	92
Table 61. Assay for sildenafil and UK-103,320 (Study 148-002).	92
Table 62. Pharmacokinetic parameters (Study 148-002).	93
Table 63. Drug supplies (Study 148-003).	94
Table 64. Assay for sildenafil and UK-103,320 (Study 148-003).	94
Table 65. Pharmacokinetic parameters (Study 148-003).	95
Table 66. Drug supplies (Study 148-004).	96
Table 67. Pharmacokinetic parameters (Study 148-004).	97
Table 68. Drug supplies (Study 148-101/101B).	99
Table 69. Demographics (Study 148-101/101B).	100
Table 70. Protocol violations (Study 148-101/101B).	100
Table 71. ITT analyses of EF question 1 (Study 148-101/101B).	101
Table 72. Drug supplies (Study 148-101C).	102
Table 73. Drug supplies (Study 148-102).	104
Table 74. Demographics (Study 148-102).	106
Table 75. Protocol violations (Study 148-102).	106
Table 76. ITT analyses of IIEF questions 3 and 4 (Study 148-102).	107
Table 77. ITT analyses of non-primary IIEF questions at week 12 (Study 148-102).	108
Table 78. Successful intercourse by event logs (Study 148-102).	109
Table 79. ITT shift analyses of IIEF questions 3 and 4 at week 24 (Study 148-102).	109
Table 80. Sub-group analyses of IIEF questions 3 and 4 (Study 148-102).	110
Table 81. Drug supplies (Study 148-103).	111
Table 82. Demographics (Study 148-103).	113
Table 83. Protocol violations (Study 148-103).	113
Table 84. ITT analyses of IIEF questions 3 and 4 (Study 148-103).	114
Table 85. ITT analyses of non-primary IIEF questions at week 12 (Study 148-103).	115
Table 86. Successful intercourse by event logs (Study 148-103).	115
Table 87. ITT shift analyses of IIEF questions 3 and 4 at week 24 (Study 148-103).	116
Table 88. Sub-group analyses of IIEF questions 3 and 4 (Study 148-103).	116
Table 89. Drug supplies (Study 148-104).	118
Table 90. Demographics (Study 148-104).	120
Table 91. Protocol violations (Study 148-104).	120
Table 92. ITT analyses of IIEF questions 3 and 4 (Study 148-104).	121
Table 93. ITT analyses of non-primary IIEF questions at week 12 (Study 148-104).	122
Table 94. Successful intercourse by event logs (Study 148-104).	122
Table 95. Drug supplies (Study 148-105).	124
Table 96. ITT analyses of Rigiscan data (Study 148-105).	125
Table 97. Plasma levels (\pm SD) of sildenafil (Study 148-105).	125
Table 98. Drug supplies (Study 148-106).	126
Table 99. Demographics (Study 148-106).	128
Table 100. Protocol violations (Study 148-106).	128
Table 101. ITT analyses of IIEF questions 3 and 4 (Study 148-106).	129
Table 102. ITT analyses of non-primary IIEF questions at week 12 (Study 148-106).	129
Table 103. Pharmacokinetic parameters after IV dosing (Study 148-203).	132
Table 104. Pharmacokinetic parameters after single and multiple dosing (Study 148-207).	137
Table 105. Pharmacokinetic parameters for sildenafil after IV and oral administration (Study 148-208).	139
Table 106. Pharmacokinetic parameters (Study 148-214).	144
Table 107. Pharmacokinetic parameters for total radioactivity after IV and oral dosing (Study 148-215).	146

Table 108. Pharmacokinetic parameters for plasma sildenafil after IV and oral dosing (Study 148-215).147	147
Table 109. Pharmacokinetic parameters for sildenafil metabolites after IV and oral dosing (Study 148-215). ...	147
Table 110. Bleeding time (Study 148-216).	150
Table 111. Pharmacokinetic parameters for sildenafil, UK-103,320, and ethanol (Study 148-217).	152
Table 112. Drug supplies (Study 148-218).	153
Table 113. Pharmacokinetic parameters for tolbutamide (Study 148-218).	154
Table 114. Urinary excretion of tolbutamide metabolites (Study 148-218).	154
Table 115. Drug supplies (Study 148-219).	155
Table 116. Bleeding time and prothrombin time (Study 148-219).	156
Table 117. Pharmacokinetic parameters (Study 148-221).	158
Table 118. Bleeding time (Study 148-222).	159
Table 119. Effects on vital signs (Study 148-225).	162
Table 120. Pharmacokinetic parameters (Study 148-226).	164
Table 121. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-227).	166
Table 122. Drug supplies (Study 148-228).	167
Table 123. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-228).	168
Table 124. Test of dose-proportionality for AUC and C _{max} of sildenafil (Study 148-228).	168
Table 125. Pharmacokinetic parameters (Study 148-229).	171
Table 126. Vital signs (Study 148-230).	173
Table 127. Vital signs (Study 148-231).	175
Table 128. Pharmacokinetic parameters (Study 148-232).	177
Table 129. Color discrimination error scores for normals (Study 148-232).	178
Table 130. Pharmacokinetic parameters (Study 148-234).	180
Table 131. Hemodynamic data at highest dose (Study 148-301).	181
Table 132. Penile plethysmography (Study 148-350).	183
Table 133. Penile plethysmography (Study 148-351).	184
Table 134. Drug supplies (Study 148-353).	186
Table 135. Demographics (Study 148-353).	187
Table 136. Protocol violations (Study 148-353).	187
Table 137. ITT analyses of global effectiveness data (Study 148-353).	187
Table 138. ITT analyses of non-primary SFQ questions at week 4 (Study 148-353).	188
Table 139. Drug supplies (Study 148-354A).	189
Table 140. Drug supplies (Study 148-355).	191
Table 141. Drug supplies (Study 148-356).	193
Table 142. Drug supplies (Study 148-357).	195
Table 143. Effectiveness data (Study 148-357).	196
Table 144. Drug supplies (Study 148-358).	197
Table 145. Drug supplies (Study 148-359).	199
Table 146. Drug supplies (Study 148-361).	203
Table 147. Demographics (Study 148-361).	204
Table 148. ITT analyses of IIEF question1 (Study 148-361).	204
Table 149. ITT analyses of non-primary IIEF questions at week 12 (Study 148-361).	205
Table 150. Drug supplies (Study 148-363).	206
Table 151. Demographics (Study 148-363).	208
Table 152. Protocol violations (Study 148-363).	208
Table 153. ITT analyses of IIEF questions 3 and 4 (Study 148-363).	209
Table 154. ITT analyses of non-primary IIEF questions at week 12 (Study 148-363).	210
Table 155. Successful intercourse by event logs (Study 148-363).	210
Table 156. Sub-group analyses of IIEF questions 3 and 4 (Study 148-363).	211
Table 157. Drug supplies (Study 148-364).	212
Table 158. Demographics (Study 148-364).	214
Table 159. Protocol violations (Study 148-364).	214
Table 160. ITT analyses of IIEF questions 3 and 4 (Study 148-364).	215

Table 161. ITT analyses of non-primary IIEF questions at week 12 (Study 148-364).216
Table 162. Successful intercourse by event logs (Study 148-364).216
Table 163. Sub-group analyses of IIEF questions 3 and 4 (Study 148-364).217
Table 164. Drug supplies (Study 148-367).218
Table 165. Demographics (Study 148-367).219
Table 166. Protocol violations (Study 148-367).220
Table 167. ITT analyses of IIEF questions at weeks 6 and 12 (Study 148-367).220

List of figures

Figure 1. Structure of sildenafil.	3
Figure 2. Metabolism of sildenafil (percentages in excreta).	17
Figure 3. Dissolution of sildenafil 100-mg tablets	23
Figure 4. Dissolution of sildenafil 25-mg tablets at 100 rpm.	23
Figure 5. Dissolution of 25-, 50-, and 100-mg tablets with and without film coating.	24
Figure 6. ECG data (Studies 148-001, -004, -201, and -201A.	53
Figure 7. Presumed pharmacological basis for actions of sildenafil.	54
Figure 8. Effect of cytochrome P450 inhibitors on metabolism of sildenafil (Report DM3).	72
Figure 9. Correlations between observed UK-103,320 formation and that predicted by CYP 3A4 and 2C9 combined (Report DM3).	72
Figure 10. Rate of formation of UK-103,320 in cell lines expressing CYP 1A2, 2C9, 2D6, 2E1, and 3A4 (Report DM3).	72
Figure 11. Partial metabolic scheme for UK-103,320 in human liver microsomes (Report DM5).	74
Figure 12. Inhibition of metabolism of testosterone and terfenadine by sildenafil (Report DM34).	74
Figure 13. Plasma levels of sildenafil and UK-103,320 (multiple studies).	76
Figure 14. Residuals from final model of sildenafil pharmacokinetics.	77
Figure 15. Covariates in model of sildenafil pharmacokinetics.	77
Figure 16. Goodness of fit for final model of sildenafil pharmacokinetics.	78
Figure 17. Goodness of fit for final model of UK-103,320 pharmacokinetics.	80
Figure 18. Selected covariate relationships in the final model of UK-103,320 pharmacokinetics.	80
Figure 19. Change in response to question 3.	82
Figure 20. Final dose-response model by baseline for question 3.	83
Figure 21. Change in response to question 4.	84
Figure 22. Final dose-response model by baseline for question 4.	84
Figure 23. Modeled dependence of selected adverse events on dose, AUC, and C_{max}	85
Figure 24. Plasma sildenafil and UK-103,320 levels (Study 148-001).	90
Figure 25. Relationships among pharmacokinetic parameters (Study 148-001).	91
Figure 26. Plasma levels of sildenafil and UK-103,320 (Study 148-002).	93
Figure 27. Plasma levels of sildenafil and UK-103,320 (Study 148-003).	95
Figure 28. Mean plasma levels of sildenafil and UK-103,320 (Study 148-004).	96
Figure 29. Pharmacokinetic parameters by dose (Study 148-004).	97
Figure 30. Pharmacodynamic effects at 800 mg, while standing (Study 148-004).	97
Figure 31. Exposure to study drug (Study 148-101C).	103
Figure 32. Disposition of subjects (Study 148-102).	107
Figure 33. Disposition of subjects (Study 148-103).	114
Figure 34. Disposition of subjects (Study 148-104).	121
Figure 35. Plasma levels of sildenafil and UK-103,320 after IV dosing (Study 148-203).	132
Figure 36. Log-log plots of C_{max} and AUC for sildenafil after IV dosing (Study 148-203).	132
Figure 37. Plasma sildenafil levels after single and multiple dosing (Study 148-207).	136
Figure 38. Single-dose AUC and C_{max} for sildenafil by dose (Study 148-207).	136
Figure 39. Plasma levels of UK-103,320 after single and multiple doses of sildenafil 75 mg (Study 148-207).	137
Figure 40. Mean plasma sildenafil after IV and oral dosing (Study 148-208).	140
Figure 41. V_{ss} and clearance by body weight (Study 148-208).	140
Figure 42. Plasma levels of sildenafil and UK-103,320 by time after dosing and degree of renal impairment (Study 148-214).	143
Figure 43. Clearance and C_{max} for sildenafil as a function of creatinine clearance (Study 148-214).	143
Figure 44. Clearance and C_{max} for sildenafil as a function of age (Study 148-214).	144
Figure 45. Plasma and whole-blood levels of total radioactivity after IV and oral dosing (Study 148-215).	146
Figure 46. Plasma levels of total radioactivity after IV and oral dosing (Study 148-215).	147
Figure 47. Plasma levels of sildenafil metabolites after IV and oral dosing (Study 148-215).	147
Figure 48. Proposed routes of metabolism for sildenafil (Study 148-215).	148
Figure 49. Plasma levels of sildenafil and UK-103,320 after sildenafil \pm ethanol (Study 148-217).	152
Figure 50. Plasma levels of ethanol after sildenafil \pm ethanol (Study 148-217).	152

Figure 51. Plasma levels of tolbutamide (Study 148-218).	154
Figure 52. Individual prothrombin times on placebo and sildenafil (Study 148-219)	156
Figure 53. Plasma levels of sildenafil and UK-103,320 (Study 148-221).	158
Figure 54. Ln(AUC) as a function of Child-Pugh score (Study 148-221).	158
Figure 55. Color discrimination scores (A) by dose and (B) by color at 200 mg (Study 148-223).	160
Figure 56. Plasma levels of sildenafil and UK-103,320 (Study 148-226).	164
Figure 57. Plasma sildenafil and UK-103,320 levels (Study 148-227).	166
Figure 58. Plasma sildenafil and UK-103,320 levels (Study 148-228).	168
Figure 59. Concentrations of sildenafil and UK-103,320 in plasma (Study 148-229).	171
Figure 60. Concentrations of sildenafil and UK-103,320 in semen (Study 148-229).	171
Figure 61. Plasma-semen relationships for sildenafil and UK-103,320 (Study 148-229).	172
Figure 62. Changes in standing blood pressure (Study 148-230).	174
Figure 63. Changes in heart rate (Study 148-230).	174
Figure 64. Changes in sitting vital signs (Study 148-231).	176
Figure 65. Color distribution of color discrimination errors on sildenafil at 2 hours (Study 148-232).	178
Figure 66. Plasma levels of sildenafil and UK-103,320 (Study 148-234).	180
Figure 67. Exposure to study drug (Study 148-354A).	190
Figure 68. Dependence of erectile response on plasma sildenafil (Study 148-360).	201
Figure 69. Disposition of subjects (Study 148-363).	209
Figure 70. Disposition of subjects (Study 148-364).	215