Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

LIST OF ABBREVIATIONS

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
AEM	Adverse Event Monitoring Database
AION	Anterior Ischaemic Optic Neuropathy
ALT	Alanine Aminotransferase (SGPT)
ASR	Annual Safety Report
AST	Aspartate Aminotransferase (SGOT)
ARIC	Atherosclerosis Risk in Communities
ARISg	Adverse Reaction Information System
ATC	Anatomical Therapeutic Chemical (WHO classification)
ATMP	Advanced Treatment Medical Products
AUC	Area Under the Time-Concentration Curve
AUC_{24}	Area Under the Time-Concentration Curve after One Day
C	Clinics
CDS	Core Data Sheet
cGMP	Cyclic Guanosine Monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Peak Concentration
CO	Clinical Overview
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CSR	Clinical Study Report
CTD	Common Technical Document
CYP	Cytochrome P-450
DCA	Data Capture Aid
DLO	Product Volume through the Russian Government Reimbursement Programme
DME	Designated Medical Events
DPC	DPC=Consumption of Pharmaceutical Products Dispensed by Regional or Local Health Authorities Directly to Patients
ECG	Electrocardiogram
ED	Erectile Dysfunction
EHS	Erection Hardness Score
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Electroretinogram
ET	Embryo Transplant
FDA	Food & Drugs Administration (USA)
FSAD	Female Sexual Arousal Disorder
GGT	Gamma Glutamyl Transferase
Gov	Government
GP	General Practitioner
GTN	Glyceryl trinitrate
H	Hospital
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HLT	Higher Level Term (MedDRA)
IB	Investigator's Brochure
IBD	International Birth Date
IMHS	International Men's Health Study
IIED	International Index of Erectile Dysfunction
INR	International Normalised Ratio

LIST OF ABBREVIATIONS

Abbreviation	Term
IVF	In Vitro Fertilisation
LDH	Lactate Dehydrogenase
LLT	Lower Level Term (MedDRA)
MAA	Market Authorisation Application
MAH	Market Authorisation Holder
MED	Male Erectile Dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MMAS	Massachusetts Male Ageing Study
MSM	Men who Have Sex with Men
NHS	National Health Service (UK)
NIH	National Institutes of Health (USA)
NAION	Non-arteritic Anterior Ischaemic Optic Neuropathy
NOAEL	No Observed Adverse Effect Level
NR	Not Reported
PAH	Pulmonary Arterial Hypertension
PDE	Phosphodiesterase
PEM	Prescription Event Monitoring
PET	Positron Emission Tomography
PfAST	Pfizer Analytical and Statistical Tool
PfAST-sd	Pfizer Analytical and Statistical Tool (signal detection)
PAH	Pulmonary Arterial Hypertension
PhV/PV	Pharmacovigilance
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PM	Post-marketing
PRN	'Pro re nata' i.e., when needed
PRO	Patient Reported Outcomes
PSUR	Periodic Safety Update Report
PT	(MedDRA) Preferred Term
QoL	Quality of Life
R	Retail
RMC	Risk Management Committee
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic-Pyruvic Transaminase (ALT)
SHIM	Sexual Health Inventory for Men
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SNHL	Sudden Neurosensory Hearing Loss
SOC	(MedDRA) System Organ Class
SQL	Standard Query Language
STD	Sexually Transmitted Diseases
$t_{½}$	Half Life
TBC	To Be Confirmed
TME	Targeted Medical Events
Vd	Volume of Distribution
WHO	World Health Organisation

LIST OF CHANGES FROM PREVIOUS VERSION

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
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Data lock point for current RMP	30 Jun 2013	Version number	3.2
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Part	Module/Annex	Description of Change
		The new version (3.2) of the risk management plan (RMP) has been prepared using the new RMP template based on the European Medicines Agency's current "Guidance on format of the risk management plan (RMP) in the EU"
Part I Product(s) Overview		New version number (3.2), new submission date, and new EMEA procedure number.
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	Sections 1.1 EPIDEMIOLOGY OF THE DISEASE and 1.2. CONCOMITANT MEDICATION(S) IN THE TARGET POPULATION, been updated.
	SII Non-clinical part of the safety specification	In Section 2.1.2 Non-clinical Safety Specification, under Safety Pharmacology Findings, the section on cardiovascular safety has been updated. Section 2.2. CONCLUSIONS ON NON-CLINICAL DATA has also been updated.
	SIII Clinical trial exposure	In Section 3.2 CLINICAL TRIAL EXPOSURE, new data tables for clinical trial exposure by age, race, dose and duration are presented.
	SIV Populations not studied in clinical trials	Sections 4.1 LIMITATIONS OF ADR DETECTION COMMON TO CLINICAL TRIAL DEVELOPMENT PROGRAMMES, and 4.2 EFFECT OF EXCLUSION CRITERIA IN THE CLINICAL TRIAL DEVELOPMENT PLAN, have been updated.
	SV Post-authorisation experience	Section 5.1 Action Taken by Regulatory Authorites and or MAH for Safety Reasons has been updated. Section 5.2.1 Method Used to Calculate Exposure, has been added to this module. In Section 5.2.2 Exposure, data tables have been updated. Information in Section 5.4.1 POTENTIAL FOR OFF LABEL USE, and Section 5.5 EPIDEMIOLOGICAL STUDY EXPOSURE has been updated.
	SVI Additional EU requirements for the safety specification	Sections 6.4.2 Preventive Measures for the Final Product(s) Being Marketed, 6.4.4 Reports of Medication Errors with the Marketed Product(s), and 6.1 SPECIFIC PAEDIATRIC ISSUES have been updated.

Part	Module/Annex	Description of Change
	SVII Identified and potential risks	Sections 7.1 NEWLY IDENTIFIED SAFETY CONCERNS (SINCE THIS MODULE WAS LAST SUBMITTED), 7.2 RECENT STUDY REPORTS WITH IMPLICATIONS FOR SAFETY CONCERNS, 7.3.1. Important Identified Risk – Nitrate Interaction, 7.4.1.2. Potential Drug Interactions, and 7.5. PHARMACOLOGICAL CLASS EFFECTS have all been updated.
	SVIII Summary of the safety concerns	Table 1. Summary of Safety Concerns had been updated.
Part III Pharmacovigilance Plan		This part contains all new information.
Part IV Plan for Post-Authorisation Efficacy Studies		There are no post-authorisation efficacy studies for sildenafil (ED) and none are planned.
Part V Risk Minimisation Measures		All sections of Part V have been updated.
Part VI Summary of RMP		All sections of Part VI have been updated.

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
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Administrative Information on the RMP

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	*Version Number of RMP When Last Submitted/or Not Applicable
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	26 Nov 2013	3.2
	SII Non-clinical part of the safety specification	26 Nov 2013	3.2
	SIII Clinical trial exposure	26 Nov 2013	3.2
	SIV Populations not studied in clinical trials	26 Nov 2013	3.2
	SV Post-authorisation experience	26 Nov 2013	3.2
	SVI Additional EU requirements for the safety specification	26 Nov 2013	3.2
	SVII Identified and potential risks	26 Nov 2013	3.2
	SVIII Summary of the safety concerns	26 Nov 2013	3.2
Part III Pharmacovigilance Plan		26 Nov 2013	3.2
Part IV Plan for Post-Authorisation Efficacy Studies		26 Nov 2013	3.2
Part V Risk Minimisation Measures		26 Nov 2013	3.2
Part VI Summary of RMP		26 Nov 2013	3.2
Part VII Annexes	**ANNEX 2** Current or proposed SmPC/PIL	26 Nov 2013	3.2
	ANNEX 3 Worldwide marketing status by country	26 Nov 2013	3.2
	ANNEX 4 Synopsis of clinical trial programme	26 Nov 2013	3.2
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	26 Nov 2013	3.2
	ANNEX 6 Protocols for proposed and on-going studies in Part III	26 Nov 2013	3.2
	ANNEX 7 Specific adverse event follow-up forms	26 Nov 2013	3.2

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	*Version Number of RMP When Last Submitted/or Not Applicable
	ANNEX 8 Protocols for studies in Part IV	26 Nov 2013	3.2
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	26 Nov 2013	3.2
	ANNEX 10 Details of proposed additional risk minimisation activities	26 Nov 2013	3.2
	ANNEX 11 Mock up examples	26 Nov 2013	3.2
	ANNEX 12 Other supporting data	26 Nov 2013	3.2

*A new RMP version number should be assigned each time any Parts/modules are updated

QPPV name	MariaGrazia Zurlo, MD
QPPV signature	[redacted]
Contact person for this RMP	
E-mail address or telephone number of contact person	

Overview of versions:

Version number of last agreed RMP:

Version number	3.1
Agreed within	Centralized Procedure

Current RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Submitted Within
Not applicable	Not applicable	Not applicable

Invented name(s) in the European Economic Area (EEA)	VIAGRA
Authorisation procedure	Centralised Procedure
Brief description of the product including:	Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.
Indication(s) in the EEA	Sildenafil (ED) is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for sildenafil (ED) to be effective, sexual stimulation is required.
Posology and route of administration in the EEA	For most patients, the recommended dose is 50 mg, taken as needed approximately one hour before sexual activity. Based on effectiveness and toleration the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.
Pharmaceutical form(s) and strengths	25, 50, 100 mg film coated, blue rounded-diamond shaped tablets

Country and date of first authorisation worldwide	USA	27 March 1998
Country and date of first launch worldwide	USA	May 1998
Country and date of first authorisation in the EEA	EU	14 September 1998
Date of issue of marketing authorisation valid throughout the European Union	EU	14 September 1998

Is the product subject to additional monitoring in the EU? Yes [ ] No [X]

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
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Indication

Sildenafil (ED) is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Sildenafil (ED) to be effective, sexual stimulation is required.

1.1. EPIDEMIOLOGY OF THE DISEASE

Incidence, Prevalence, Demographics of the Target Population – Age, Sex, Race/Ethnic Origin, Mortality and Morbidity (Natural History)

Estimating the frequency of male erectile dysfunction (ED) can be difficult given the reluctance of patients to seek treatment. Treatment-seeking behaviour of European patients with ED has been the subject of observational studies. These studies have shown that in Europe men are reluctant presenting to their physician for an embarrassingly perceived sex-related issue.[1,2,3] As a result, only a small proportion of men suffering from ED ever visit their physician to request treatment, and those who do are often reluctant to put themselves through the ordeal of returning every time they need a new prescription.

Even among men who are actively seeking information on ED, many resist discussing their condition with either their partner or their physician.[4] Besides their own embarrassment, 71% of men with ED thought that their physician would be unsympathetic and 68% were afraid that asking for help for sexual dysfunction would embarrass their physician, as well.[5]

Given that ED is likely underdiagnosed, most prevalence estimates are derived from population-based or clinic-based surveys.

The prevalence of moderate to severe ED in men in their 50s is approximately 25%, and this prevalence is approximately 45% for men in their 60s.[6,7,8,9] Population-based prevalence studies conducted in 12 countries indicate that 50% to 70% of men over the age of 50 years have ED, classified as minimal, moderate, or severe according to the International Index of Erectile Function (IIEF)-5 score, of erectile dysfunction (ED).

In the 2011 US National Health and Wellness Survey, 24.6% overall of male respondents aged 40+ years, self-reported ED. Among those with self-reported ED, 10.4% were aged 40-44 years, 26.8% were aged 45-54 years, 29.8% were aged 55-64 years, 19.1% were aged 65-74 years, and 13.8% were aged 75+ years; 73.6% were Caucasian, 9.9% were African American, and 11.4% were Hispanic.[10] In a cross-sectional analysis of male patients identified from 6 US academic clinics during 2000-2002, 27% of 4,108 completing a single-question ED assessment based on the Massachusetts Male Aging Study (MMAS) had moderately severe ED and 42% had complete ED; the prevalence of moderate-to-severe ED was 56% in the subset of 1,659 patients who completed the IIEF assessment.[11] In the Global Online Sexuality Survey (GOSS) completed by 2,022 US males identified online for participation during 2011-2012, the prevalence of ED was 37.7% overall and increased with age; 23.6% reported ED among respondents aged 40-49 years, 30.8% among respondents aged 50-59 years, and 57.4% among respondents aged 60+ years.[12]

In a set of 2 population-based surveys conducted in Sweden in 1992 and 2003, 44.1% reported ED in 1992 (n = 7,763) while 51.3% reported ED in 2003 (n = 7,349).[13]

In a recent population-based survey of Australian residents of 101,674 men with no prior prostate cancer, aged 45+ years, 25.1% had mild ED, 18.8% had moderate ED, and 16.8% had complete ED.[14]

A survey of 950 male Hong Kong residents identified from 1 outpatient clinic in 2010-2011 showed higher prevalence estimates; 13% reported mild ED, 14% reported mild-to-moderate ED, 16% had moderate ED; and 24% had severe ED (ED was measured using a modified version of the IIEF).[15]

Among 27,839 male residents of the US, UK, Germany, Italy, Spain, Mexico, and Brazil interviewed as part of the Men's Attitudes to Life Events and Sexuality (MALES) study, 16% reported ED (the highest prevalence, 22%, was noted among US respondents, while the lowest prevalence, 10%, was noted among respondents from Spain.[16]

Many doctors do not usually raise the subject of sexual health. It is not part of formal health screening for men in the majority of countries and is generally not considered a medical priority. For many men the loss of erectile function can have significant consequences for their relationship with their partners and their self-esteem.[17,18] ED is associated with depression[19] and can adversely influence personal relationships.[1] Consequently, the benefits of a successful treatment of ED extend beyond the restoration of sexual function, as indicated by improved depression rating scores, a general improvement in couple relationships, and an overall improved quality of life.[20,21,22,23,24]

Risk Factors for the Disease

As most epidemiology data arise from cross-sectional surveys, the temporal relationship between factors that increase the risk and the occurrence of ED cannot be satisfactorily addressed. Information on underlying comorbidities, including diabetes, obesity, hypertension, and the clinical manifestations of atherosclerosis (see Section 1.3 below), are relevant to the assessment of ED risk, as ED is often associated with a vascular disease and is often a marker of the progression of the underlying conditions exemplified above.

Main Treatment Options

Currently employed medical interventions for the management of ED include oral therapies that target the penis through phosphodiesterase type 5 (PDE5) inhibition and intrapenile therapies (intra-urethral suppositories and intracavernous injections). The vacuum constriction device is a noninvasive mechanical device. Surgical therapies include implantation of prosthetic devices and vascular surgeries. Psychosexual therapy may be useful in combination with both medical and surgical treatment for men with ED. For some patients, brief education, support, and reassurance may be sufficient to restore sexual function, while for others, referral to more specialized and intensive counseling may be necessary. Oral phosphodiesterase type 5 inhibitors, sildenafil, tadalafil, and vardenafil unless contraindicated are considered first-line of therapy for erectile dysfunction.[25]

1.2. CONCOMITANT MEDICATION(S) IN THE TARGET POPULATION

Most common concomitant medications (≥10% by WHO-Drug Anatomical Therapeutic Chemical (ATC) 2 Term) taken by patients in parallel studies were common analgesics, agents acting on the renin-angiotensin sytem, antidiabetic drugs, stomatological preparation, lipid-lowering and anti-thrombotic agents, ophthalmologicals, calcium-channel blockers, beta-blocking agents, anti-inflammatory and antirheumatic products, vitamins, and diuretics (see MAA Table 7.1.1 for complete list of concomitant medications from all 74 double-blind placebo-controlled studies). Thus, in addition to relevant underlying medical conditions, many of the listed concomitant medications have the potential for negatively affecting the sexual function of the male subject.

1.3. IMPORTANT CO-MORBIDITIES FOUND IN THE TARGET POPULATION

Data from Malaysia, Italy, Brazil and Japan indicate that 38% of men with ED reported two or more risk factors for cardiovascular disease, compared with only 19% of men of the same age without self-reported ED.[26,27,28,29] The most common aetiologies of ED are vascular, neurologic, iatrogenic and psychogenic. The primary aetiology is thought to be organic in approximately 80% of patients with ED.

ED shares a number of risk factors with cardiovascular disease and premature mortality, including increasing age, diabetes, hypertension, dyslipidaemia, smoking, and excessive alcohol consumption.[30,31,32] ED is often a vascular condition and is often a marker of a more advanced stage of each of these diseases. More recently, analysis of the 2011 US National Health and Wellness Survey showed that among those with self-reported ED, 50% had hypertension, 27.4% had diabetes, 30.0% had sleep difficulties, and 22.8% were currently smoking.[10]

Among the 37.7% of 2,022 US males participating in the Global Online Sexuality Survey (GOSS) who reported having ED, 9.4% reported having diabetes, 17.9% reported having been treated for hypertension, 37.0% were obese, 17.6% reported smoking, and 51.5% reported consistent alcohol use.[12]

In a recent population-based survey of Australian residents of 101,674 men with no prior prostate cancer, aged 45+ years, the proportion of men reporting moderate/complete ED was 62.5% in those who reported having been diagnosed with diabetes, 49.1% in those who reported having been diagnosed with hypertension, 45.6% in those who reporting having been diagnosed with high cholesterol.[14]

Among 27,839 male residents of the US, UK, Germany, Italy, Spain, Mexico, and Brazil interviewed as part of the Men's Attitudes to Life Events and Sexuality (MALES) study, increasing age, hypertension, heart trouble/angina, high cholesterol, diabetes, and depression were more prevalent in men reporting ED as compared with men reporting no ED.[16]

With regard to hypertension, data suggest that treatment of ED may also help reduce the severity of hypertension. In this respect, a recent study indicated that the proportion of subjects achieving body mass indexes <25 kg/m^2 increased slightly after treatment for ED,

particularly in those with the highest blood pressure.[33] It should be noted also that PDE5 inhibitors are hypotensive agents and are used, for example, in the treatment of pulmonary hypertension.

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PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

2.1. NON-CLINICAL

2.1.1. General

A full discussion of non-clinical studies is provided in the original Marketing Authorisation Application (MAA) for sildenafil for the treatment of erectile dysfunction (ED).

Sildenafil is a selective inhibitor of phosphodiesterase-5 (PDE5). In the corpus cavernosum, as a consequence of the selective inhibition of this enzyme, sildenafil leads to increased levels of cyclic guanosine monophosphate (cGMP) and consequently relaxation of vascular smooth muscle. The main potential or theoretical safety issues for sildenafil relate to the pharmacological effects arising from the elevation of cGMP in other tissues such as systemic vascular smooth muscle, the retina, platelets, and gastrointestinal smooth muscle. The safety pharmacology studies are unremarkable except for a moderate antagonist affinity of sildenafil for adenosine A2a receptors, although this finding is unlikely to have any functional consequences.

Oral absorption of sildenafil is rapid and high in all species. Systemic bioavailability is attenuated by pre-systemic hepatic metabolism to an extent consistent with the plasma clearance value in each species. UK-103,320 is the major metabolite of sildenafil. A species-specific gender difference in pharmacokinetics in the rat reflects the more rapid metabolism to UK-103,320 in males. Volume of distribution (Vd) is similar in rodents and humans but is higher in the dog, probably reflecting the lower plasma protein binding in this species. The pattern of tissue distribution of drug-derived radioactivity in the rat is as expected for a lipophilic weak base, including an affinity for melanin, which is believed to be of no toxicological significance. In all species studied, clearance of sildenafil is via 5 principal pathways of oxidative metabolism, the majority of the dose being excreted in the faeces over 48 hours. Plasma drug concentrations in man increase linearly over the clinical dose range and metabolism is mediated by CYP3A4 and CYP2C9, the former appearing to be more important at clinical doses. Circulating metabolites are present, but only one (UK-103,320) would be expected to make a contribution to therapeutic activity and, moreover, a minor contribution relative to sildenafil itself. Interactions with co-administered agents are unlikely to be of clinical significance since both sildenafil and UK-103,320 are only weak inhibitors of major human drug-metabolising P450s. Toxicokinetic data for both sildenafil and UK-103,320 indicate a large separation between plasma exposure to drug-related components in man and that associated with toxicity in the rat and the dog.

2.1.2. Non-clinical Safety Specification

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Toxicity	
Single Dose Toxicity	The administration of single oral doses of sildenafil indicated a minimal lethal dose of 500-1000 mg/kg in mice and 300-500 mg/kg in rats.
Repeated Dose Toxicity	In repeated oral dose studies in rats and dogs, doses were limited by isolated deaths at 200 mg/kg in rats and by gastric intolerance in dogs at 80 mg/kg. The main effects of treatment in rats were adaptive liver changes (associated with thyroid follicular hypertrophy). In dogs, heart rate was moderately increased in all studies, with no consistent changes in blood pressure. In chronic dog studies, 50 mg/kg was associated with Idiopathic Juvenile Arteritis (Beagle Pain Syndrome), a syndrome thought to be an expression of a latent disease precipitated by stress, rather than a direct toxic effect of the compound. Oral doses of sildenafil not producing adverse effects are therefore 60 mg/kg in rats and 15 mg/kg in dogs.
Carcinogenicity	Sildenafil did not induce mutations in bacterial or mammalian cells in vitro, nor did it cause clastogenic activity in vivo or in vitro. There was no evidence of a carcinogenic effect in mice. Mortality in mice at 5, 10 and 30 mg/kg was often associated with gastrointestinal dilation. Investigative studies have shown that mice are particularly sensitive to effects of sildenafil on the gastrointestinal tract. In rats, 60 mg/kg produced an increased incidence of proliferative changes in the thyroid, resulting from the liver adaptive changes, but as in mice, no carcinogenic effects. These studies indicate that sildenafil has no carcinogenic potential for man.
Teratogenicity	Sildenafil had no adverse effects on fertility and has no teratogenic potential.
Reproductive Toxicity	The main findings in the pre- and postnatal study were limited to the high dose group (60 mg/kg). The mechanism responsible for these high dose effects is unlikely to be linked to a diminished blood supply to the uterus and placenta. It may be related to the inhibition of oxytocin-induced contractions in the rat uterus, demonstrated in vitro. The estimated exposure for high-dose pregnant female rats in the pre-and postnatal study was about 50 fold greater than clinically relevant plasma concentrations. Therefore, the high-dose effects in the pre- and postnatal study were not considered to be indicative of a potential safety risk for the intended patient population. The effects at the high dose of 60 mg/kg consisted of minimal maternal toxicity characterized by a significant decrease in the ratio of viable pups compared to controls. Consequently, the litter size at birth (viable pups) at the high dose was significantly decreased. In F1 high-dose pups, statistically significant decreases were seen in 4-day survival index (92.2% compared to 99.3% in control), and pup weight on Day 1 post-partum (pp) in both sexes (-9% relative to controls). There were slight delays at the high dose in the appearance of upper incisors (both sexes), the attainment of air righting reflex (male pups) and the attainment of surface righting (female pups). An analysis of covariance, taking pup body weight on Day 1 pp as covariant and using SAS procedure MIXED, showed no statistical differences from

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
	controls for these developmental landmarks at the high dose. This analysis confirms that these observations were related to decreased pup body weight. The available data do not support the possibility that the effects observed at the high dose in the pre- and postnatal study result from the vasodilatory properties of sildenafil that would cause an increased peripheral blood perfusion leading to a diminished blood supply to the uterus and placenta. Digital abnormalities are well-established foetal findings associated with haemodynamic changes induced by vasodilating drugs (nifedipine, phenytoin, nitrendipine, felodipine and hydralazine) or by hypoxia (clamping of the uterine vessels). In rabbit foetuses, haemodynamic changes were associated with oedema, haemorrhage, reduction (hypoplasia) of the distal phalanges, abnormal structure of the distal phalanges, fusion of the distal phalanges and necrosis of the developed cartilage in the phalanges. In rat foetuses, hypoxia was associated with hypoplasia of the nails and distal phalanges, haemorrhage and/or tissue necrosis of extremities (nose, limbs, tail and genital tubercle). Gross findings of vasodilatation or digital abnormalities indicative of haemodynamic changes/hypoxia were not observed in fetuses from embryo/foetal development studies (Nos. 95058/95059 and 95043/95044) or in pups from the pre- and postnatal development study (No. 95068/95095) with sildenafil. Although plasma concentrations of sildenafil were not measured in the pre- and postnatal study, exposure levels can be estimated using toxicokinetic results from other toxicology studies. These estimates are compared to the human free C_{max} and AUC_{24} of 4.3 ng/mL and 57 ng•h/mL, respectively at the therapeutic dose of 20 mg TID. When using an estimated AUC based on free AUC value (2705 ng•h/mL) in females at 60 mg/kg in the 6-month rat study (No. 91098), the exposure multiple is about 50. The corresponding free C_{max} in the 6-month rat study was 422 ng/mL (Total C_{max} 8440ng/mL, free fraction of 5%), yielding an exposure multiple of about 100. This value is consistent with the multiples of 66 to 110 calculated from the range of concentrations (5650 - 9570 ng/mL) in pregnant rats given 50 mg/kg in embryo/fetal developmental study (No. 95058/59). Sildenafil is a potent, orally active, selective inhibitor of cyclic guanosine monophosphate (cGMP) specific PDE5. PDE5 is ubiquitous to vascular smooth muscle including that of the uterine vasculature. If related to pharmacology, the effects observed in the pre- and postnatal development study would be expected to be present in a variety of tissues at lower doses, where pharmacologically active exposure were achieved. Furthermore, the potential utility of sildenafil in the treatment of pre-eclampsia (PET) and Intrauterine growth restriction (IUGR) is under investigation in a Phase 2 clinical trial. It is believed that the NO-cGMP pathway may be important in producing uterine arterial vasodilatation, which is anticipated to be of benefit in PET and IUGR associated with placental insufficiency and uterine vasoconstriction. The different sources of supportive data suggest that the blood supply to the uterus or the placenta is increased, not diminished following sildenafil administration. In oophorectomised sheep, replacement of estradiol significantly improved uterine blood flow compared to baseline. Concomitant intravenous administration of sildenafil further significantly potentiates this increased uterine blood flow with little effect in the absence of estradiol. In healthy mini-pigs, another PDE5 inhibitor (UK-343,664) administered intravenously on Day 2 post-ovulation has been shown to produce a significant improvement in uterine blood flow without dramatic effects on mean arterial blood pressure (in-house data, unpublished). In a rat model of induced hypoxia, sildenafil

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
	produced a significant increase in fetal weight with short duration hypoxia, compared to placebo. In longer duration of hypoxia, sildenafil was able to maintain fetal weight whereas fetal weight decreased in its absence. The presumption is that this was mediated via improved uterine blood flow. The mechanism involved in the high dose effects observed in the pre- and postnatal study may be related to inhibition of oxytocin-induced contractions in the rat uterus, demonstrated in vitro. The high concentration used in that study (10 µM or 4746 ng/mL) is close to the range of peak plasma concentrations expected in pregnant rats receiving a dose of 60 mg/kg, based on the plasma concentrations in pregnant rats given 50 mg/kg in embryo/fetal developmental study (No. 95058/59) (5650-9570 ng/mL at 50 mg/kg).
	In summary, a number of findings (litter size, pup weight at birth and 4-day survival index) in the pre and postnatal study in rats were considered as high-dose effects of sildenafil. These effects were observed at plasma exposures 50-fold greater than measured at the therapeutic dose in humans (20 mg TID). The identified developmental landmarks were secondary to changes in pup body weight at the high-dose and had a similar incidence to historical control data at the mid and low doses. The mechanism responsible for these high dose effects may be related to the inhibition of oxytocin-induced contractions in the rat uterus, demonstrated in vitro. A diminished blood supply to the uterus and placenta is considered unlikely as: a) sildenafil does not produce foetal effects associated with reduced utero-placental blood flow following administration of a vasodilator; b) the available in-house and reported data suggest utero-placental blood flow is increased. Consequently, the results seen at exposures well in excess of the human exposure in the pre-and postnatal development study were not considered to be indicative of a potential safety risk for the intended patient population. The estimated exposure for high dose pregnant female rats in the pre-and postnatal study was about 50 fold greater than clinically relevant plasma concentrations[a]. A clinical specification for sildenafil (ED) use in pregnancy is discussed in Part II Module SIV.
Paediatric Toxicity	Sildenafil (ED) is not indicated for use in a paediatric patient population (ie, <18 years of age). Refer to the sildenafil (PAH) Risk Management Plan for further discussion of clinical studies conducted to support the clinical development of sildenafil (PAH) in the paediatric patient population affected by pulmonary arterial hypertension (PAH).

[a] Estimated peak plasma concentration based on the plasma concentrations (5650-9570 ng/mL) in pregnant rats given 50 mg/kg in embryo/fetal developmental study (No. 95058/59). Estimated AUC based on free AUC value (2705 ng•h/mL) in females at 60 mg/kg in the 6-month rat study (no. 91098). Human free C_{max} and AUC of 4.3 ng/mL and 57 ng•h/mL respectively at the therapeutic dose of 20 mg TID (Table 5, Nonclinical Overview). Free fraction of 4% in human and 5% in rat.

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Safety Pharmacology Findings	
Cardiovascular Safety	Unlike the phosphodiesterase-3 (PDE3) inhibitor milrinone, sildenafil had no inotropic action on the dog-isolated trabeculae [1] or rabbit isolated papillary muscle,[2] at up to 10 μM. Furthermore, sildenafil did not alter isoprenaline-induced increases in contractility in rabbit papillary muscle, as would be expected of an inhibitor of PDE3, up to 1 μM. However, sildenafil (10 μM) did potentiate isoprenaline-induced contractility at 10 μM. Hence, sildenafil does not change levels of cyclic adenosine monophosphate (cAMP) in the dog coronary artery or exhibit inotropic activity expected from a PDE3 inhibitor at concentrations up to 1 μM (286-fold the PDE5 inhibitory concentration and between 24- and 111-fold the effective free plasma concentrations in pulmonary hypertension in man). Preclinical studies demonstrate that sildenafil is a pulmonary vasodilator over a therapeutic concentration range with only small systemic vasodilator effects [1]. This results in decreased pulmonary artery pressure and a reduction in pulmonary vascular resistance. Therefore, outflow resistance from the right ventricle is ameliorated and the load on the right ventricular muscle is relieved. Furthermore, left heart filling pressures will also be reduced, thereby helping to maintain left ventricular performance. The haemodynamic profile of sildenafil in pulmonary arterial hypertension (PAH) patients (Study 1481024) confirms that pulmonary artery pressure and pulmonary vascular resistance are indeed reduced.

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Ocular Non-Clinical safety Specification	The expression of phosphodiesterase-6 (PDE6) has been confirmed in the retina of man, dog and rat, and is inhibited by sildenafil over the same concentration range.[3] Functional changes to the retina with sildenafil have been investigated using electroretinogram (ERG) recordings in the dog, and have demonstrated effects which were reversible and proportional to plasma sildenafil concentrations. However, sildenafil only affected the ERG at plasma concentrations higher than those active on the pulmonary vasculature in the anaesthetised dog. Furthermore in rat and dog toxicology studies, plasma exposure levels of sildenafil, which are pharmacologically active on the retina, did not cause structural changes to the retina.[4] Ophthalmologic examinations have revealed no unusual findings in rats, mice or dogs treated up to 24, 18 or 12 months respectively. A thorough in-depth histopathological assessment of the structural integrity of the retina was conducted in rat and dog toxicology studies of up to 2 years in duration. A detailed qualitative examination of histologic sections of eyes was performed together with a histomorphometric analysis of the nuclear layers of the retina in the 6-month and carcinogenicity rat studies, and in the 6- and 12-month dog studies. There was no evidence of an alteration of the integrity of the retina. Histologically, the retina is subdivided into well-defined layers that can be easily identified. The photoreceptor layer or rod and cone layer is the outermost layer. It is composed of the highly differentiated portion of the cytoplasm of photoreceptor cells that contains the photopigments that initiate the excitatory visual response to light. The next layer, the outer nuclear layer is separated from the inner nuclear layer by the outer plexiform layer. The cell body of photoreceptor cells are in the outer nuclear layer, their axon synapse with the dendrites of neurons in the outer plexiform layer, the cell body of these neurons is in the inner nuclear layer. The outer and inner nuclear layers are identified morphologically by the crowded layers cell nuclei that are stained in blue on Hematoxylin and Eosin sections. Histopathologically, degeneration of photoreceptor cells may manifest itself as various degrees of morphological alterations affecting the cytoplasm (eg, vacuolation, shrinkage, thinning, discolouration) and/or the nucleus (eg, picnosis, vacuolation, apoptosis) and ultimately as a loss of photoreceptor cells. Loss of photoreceptor cells is evident as a reduction in the number of nuclei in the outer nuclear layer. Typically in early or mild cases, inner retina layers remain intact. Because of the considerable interconnection between cells within and between retina layers, inner layers may be affected with time and/or increased severity. The changes described above would be typically detected when the pathologist examines the retina under the microscope. Nuclear assessment has been carried out for Study Nos. 91098 (6-month oral rat,) and 94092 (24-month carcinogenicity). The results indicate that there is no evidence of an effect of treatment on the retina in either study.[5,6] Similarly, the retina of dogs which contains both rods and cones, from Study Nos. 91099 (6-month oral dog) and 95039 (12-month oral dog) also had no effect.[7,8] Both the inner and outer nuclear layers were counted in dogs because damage to cones is reflected in the inner nuclear layer. The results indicate that there is no evidence of an effect of treatment on the retina in either study. The rat retina is dominated by rods and thus counting of the inner nuclear layers is not appropriate.

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
	In conclusion, the integrity of the retina, including the photoreceptor cells, was directly fully assessed by histopathological examination of the retina conducted in rat and dog toxicology studies of up to 2 years in duration. There was no evidence of an adverse effect of sildenafil in the retina of rat or dog. An ocular clinical specification is discussed in Part II Module SVII. An ocular pharmacovigilance plan to further assess safety in patients who are treated with sildenafil for erectile dysfunction is discussed in Part III.
Non-arteritic anterior ischaemic optic neuropathy (NAION)	Non-arteritic anterior ischaemic optic neuropathy (NAION) has been reported rarely post-marketing in temporal association with the use of all phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil (ED). It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Bernstein et al (2003)[9] published a paper describing a model of NAION in Sprague-Dawley rats. The authors selectively thrombosed the microvessels supplying the optic nerve by directly photoactivating rose Bengal with a laser. Induced histological optic nerve changes were apparent 6 days after treatment, with axonal swelling and collapse. Myelin sheath breakdown was prominent by Day 11, while permanent changes included stromal scarring and axonal loss that were apparent 90 days after induction of NAION. Histological changes in the retina were apparent 37 days after NAION induction, with a reduction in the number of retinal ganglion cells (RGC) and an increased spacing of RGCs. Other retina layers were morphologically unchanged. Quantification of the number of RGCs confirmed the decline in their number. No information was presented on the longer-term changes in the retina. Overall, the authors concluded that the rat model resembles human anterior ischaemic optic neuropathy (AION) functionally and morphologically. Retinal ganglion cells are the terminal link of the neural network of the retina, their cell body is located in the ganglion cell layer of the retina, the innermost layer, and their axons become the fibers of the optic nerve, conducting the results of the retina activity to the brain. RGCs are present as one cell layer in the rat. The histopathological examination in rat and dog toxicology studies of sildenafil involved all the major structures of the visual pathways with the exception of the optic radiation in the rat brain due to its short longitudinal dimension. These included all layers of the retina and the optic nerve. Histopathology did not reveal any evidence of a treatment-related effect, there being no evidence of morphological alterations or clinical abnormalities. There was no evidence of an effect of treatment on the retina, optic nerve or associated blood vessels in either species. There were no pathological changes that would suggest the occurrence of a syndrome similar to that in the rat model of NAION described by Bernstein et al (2003).[9] The absence of effect was confirmed by an independent peer review of the histopathology sections of eye from four toxicity studies in dogs, from one month to one year in duration, and one 6-month toxicity study in rats. Importantly, mice, rats and dogs were exposed for prolonged periods to plasma concentrations of sildenafil or its active metabolite, UK-103,320, which are known to affect retinal function (ERG or isolated retina) in the dog.

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
	In conclusion, administering doses of sildenafil in excess of those shown to be pharmacologically active in the retina, daily for up to 24 months, does not result in any treatment-related toxicity of the retina or eye. NAION is discussed as a clinical safety specification in Part II Module SVII.
Bleeding	In preclinical studies, sildenafil at 0.3 mg/kg IV (t = 25 min) increased the rat tail bleeding time by approximately 60 %, although this change was not statistically significant. In rabbits 1 mg/kg IV significantly prolonged bleeding time. Sildenafil's increase in bleeding time was additive with that of heparin but not synergistic with heparin or aspirin. The doses used were approximately 20 times higher than the effective dose on the corpus cavernosum pressure in dogs conducted to support the use of sildenafil for male erectile dysfunction. Sildenafil had no effect on clotting time in rats and rabbits. Clinical experience with sildenafil (ED) provides more useful data on bleeding risk in man than further laboratory animal studies. The effects of sildenafil (ED) on bleeding time and platelet aggregation are discussed in Summary of Clinical Pharmacology of the sildenafil (ED) MAA.[10] Overall, single oral doses of sildenafil (ED) above 15 mg were generally associated with a potentiation of the anti-aggregatory effects of sodium nitroprusside (SNP), on adenosine diphosphate (ADP) aggregation of ex vivo platelets (Studies 148-201, 148-201A and 148-206). Sildenafil (ED) had no effect on other ex vivo tests (ADP-induced platelet aggregation of whole blood and ADP-induced aggregation of platelet-rich plasma in the absence of SNP). These findings confirm that sildenafil (ED) has no direct effect on platelet function ex vivo, but will potentiate the action of a NO donor, SNP. These data are consistent with the need for a NO drive to exist before sildenafil (ED) produces its pharmacological effect (Study 148-206) on platelets. These modest effects on platelet activity, *ex vivo*, did not result in a clinically significant effect on bleeding time in healthy volunteers (Study 148-206). The absence of a clinical effect on bleeding time was also demonstrated when sildenafil (ED) was co-administered with aspirin (Studies 148-216 and 148-222, discussed in the sildenafil (ED) MAA.[11] Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil (ED) was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated. A potential safety risk exists in relation to anti-platelet effects of sildenafil (ED) in the presence of an NO donor. However, as nitrates are contraindicated with sildenafil (ED), a bleeding risk should remain a potential one. In conclusion, there is no evidence that sildenafil (ED) prolongs bleeding time or inhibits platelet aggregation on its own in humans, and in this respect, the animal data do not predict the human situation.

2.2. CONCLUSIONS ON NON-CLINICAL DATA

Safety Concerns	
Important identified risks (confirmed by clinical data)	Nitrate Interaction
Important potential risks (not refuted by clinical data or which are of unknown significance)	None.
Missing information	None.
New identified safety concern	None.

References

[1] Sildenafil Toxico-Pharmcological Expert Report, Section 2.2.4

[2] Revatio Oral MAA Pharmacology Written Summaries, Module 2.6.2.3.4, Study No. P76

[3] Sidenafil Toxico-Pharmcological Expert Report, Section 2.2.6

[4] Sildenafil Toxico-Pharmcological Expert Report, Section 5, Ocular Safety in Clinical Studies

[5] [redacted] Review of sections of eyes from four toxicity studies conducted in beagle dogs and one toxicity study conducted in rats. Unpublished report 1997, K96/033.

[6] [redacted]. Examination of sections of eyes from a 24 month toxicity study in rats with sildenafil. Unpublished report 1998c, K98/006c.

[7] [redacted] Examination of sections of eyes from a 6 month toxicity study in beagle dogs with sildenafil. Unpublished report 1998a, K98/006A.

[8] [redacted] Examination of sections of eyes from a 12 month toxicity study in beagle dogs with sildenafil. Unpublished report 1998b, K98/006B.

[9] Bernstein SL; Guo Y, Kelman SE; Flower RW; Johnson MA. Functional and cellular responses in a novel rodent model of anterior ischaemic optic neuropathy. *Investigative Ophthalmology and Visual Science* 2003; 44: 4153-62.

[10] Revatio Oral MAA, Summary of Clinical Pharmacology Module 2, Section 2.7.2.

[11] Revatio Oral MAA, Summary of Clinical Pharmacology Module 2, Section 2.7.2.3.4.1

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

3.1. BRIEF OVERVIEW OF DEVELOPMENT

3.2. CLINICAL TRIAL EXPOSURE

Tables 1- 4 present the exposure data from all 136 completed sildenafil (ED) studies including 54 non-placebo-controlled, parent and extension studies in the MAH clinical trial repository.

3.2.1. Clinical trial exposure in all completed sildenafil (ED) studies in by age, race, dose and duration (N=136) [a]

Table 1. Duration of Exposure (Totals)

Total Exposed Population

Duration of Exposure (at Least)	Persons	Person Time(Years)[a]
Cumulative up to 1 month	6186	700.90
Cumulative up to 3 months	19731	3641.42
Cumulative up to 6 months	21931	5089.51
Cumulative up to 12 months	23101	8338.01
Cumulative >12 months	81	4627.18

Exposure was episodic, as needed, during the reported exposure period.
a. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.
Source: SCS 1371.b, Table 25.6.1.

[a] Source: 148-101B, 148-101C, 148-102, 148-102C, 148-103, 148-103C, 148-104, 148-104C, 148-105, 148-105C, 148-106, 148-106C, 148-107, 148-108, 148-109, 148-110, 148-351, 148-353, 148-354A, 148-354B, 148-354C, 148-355, 148-356, 148-357, 148-358, 148-359, 148-360, 148-361, 148-363, 148-364, 148-365, 148-350, 148-366, 148-367, 148-367B, 148-369, 148-369C, 148-370, 148-373, 148-378, 148-379, 148-803, 166-301, A1481006, A1481030, A1481036, A1481041, A1481042, A1481074, A1481084, A1481085, A1481090, A1481122, R-0529, R-0530, R-0538, R-0539, R-0540, SDN-AFME-98-001, SDN-AFME-98-003, SDN-AFME-98-004, SDN-B-98-001, SDN-BRA-98-001, SDN-BRA-98-002, SDN-BRA-98-003, SDN-BRA-98-004, SDN-BRA-98-006, SDN-BRA-98-007, SDN-CDN-98-001, SDN-CDN-98-002, SDN-CZ-98-001, SDN-D-98-002, SDN-E-98-001, SDN-E-98-002, SDN-E-98-003, SDN-JP-96-601, SDN-JP-96-602, SDN-K-98-001, SDN-LA-97-001, SDN-LA-97-003, SDN-MEX-98-001, SDN-NL-98-002, SDN-NY-96-002, SDN-NY-96-003, SDN-NY-96-004, SDN-NY-96-005, SDN-NY-96-006, SDN-NY-97-001, SDN-NY-97-002, SDN-NY-97-004 SDN-NY-98-001, SDN-NY-98-002, SDN-NY-98-003, SDN-RU-98-001, SDN-S-98-001, SDN-F-98-001, SDN-BRA-98-005, A1481104, A1481118, A1481119, A1481120, A1481137, A1481031, A1481146, A1481177, A1481217, A1481179, A1481068, A1481132, A1481163, A1481183, A1481037, A1481103, A1481161, SDN-E-98-004, SDN-E-98-005, A1481195, A1481222, A1481230, A1481236, A1481240, A1481239, A1481247, A1481025, A1481048, A1481238, A1481237, A1481210, A1481251, A1481110, A1481047, SDN-F-98-002, SDN-98-F-003, A1481070, A1481108, A1481187.
Subjects enrolled in more than one study (i.e., parent study and one or more follow-up studies) are counted only once. Their exposure to sildenafil (ED) is reported as cumulative number of days/years across both parent and follow-up study.

Table 2. By Modal Dose (Totals)

Total Population		
Dose of Exposure (Modal Dose)[a]	**Persons**	**Person Time(Years)[b]**
Total population		
5 mg	27	12.40
10 mg	38	4.44
25 mg	637	529.49
50 mg	9831	3605.62
75 mg	43	20.10
100 mg	12,558	8739.33
200 mg	48	11.32
Total	23,182	12,965.19

Exposure was episodic, as needed, during the reported exposure period.
a. Modal dose = the dose patient was exposed to the longest period of time. If there were ties, the highest dose (between the two) was selected. Modal dose for subjects participating in both parent and follow-up studies was estimated based on cumulative exposure across parent and follow-up study.
b. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25
Source: SCS 1371b, Table 25.5.1.

Table 3. By Age Group (Totals)

Total Population		
Age Group	**Persons (Total number of UNIQUE subjects)**	**Person Time(Years)[a]**
≤65 years	19176	10593.25
>65 years	3937	2362.21
Missing	69	9.72
Total	23182	12965.19
≤ 18 years	4	0.87
> 18 to ≤ 65 years	19172	10592.39
> 65 to ≤ 75 years	3573	2190.84
>75 years	364	171.84
Missing	69	9.72

Exposure was episodic, as needed, during the reported exposure period.
a Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25
Source: SCS 1371b, Table 25.3.1 and 1529, Table 3.0

Table 4. By Ethnic or Racial Origin (Totals)

Total Population		
Ethnic/racial Origin	**Persons**	**Person Time(Years)** [a]
Caucasian	16044	10996.62
Black	1517	692.07
Asian	1695	371.06
American Indian	1174	346.96
Latin American	925	225.81
Missing	1827	332.67
Total	23182	12965.19

Exposure was episodic, as needed, during the reported exposure period.
a. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.
Source: SCS 1371b, Table 15.4.1

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

4.1. LIMITATIONS OF ADR DETECTION COMMON TO CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	Only 23,182 patients were exposed to sildenafil (ED) in clinical trials of male patients with erectile dysfunction (ED). 9570 patients were exposed in double-blind studies.	Clinical trial safety database is relatively limited in terms of its ability to identify rare ADRs.
Due to prolonged exposure	Only 23,182 men were exposed to sildenafil (ED) for a cumulative duration of 12,965 years in clinical trials. Because individual patient exposure during clinical trials was intermittent, information about adverse events due to continuous exposure is not available.	The effects of prolonged continuous exposure are unknown and they could not be assessed in the clinical program.
Due to cumulative effects	Since sildenafil has a relatively short half-life (4-5 hours) and its posology in ED is OD prn, cumulative effects are not expected.	In clinical trials, subjects were instructed to take no more than 1 tablet of assigned dose per day. Short half life of sildenafil (ED) and studied dose regimen (intermittent use on an as-needed basis) would not allow for assessment of cumulative effects in clinical program.
Which have a long latency	Typical study duration was 8 to 12 weeks. Some studies had an open-label period of up to 12 mos.	Clinical studies of sildenafil to date do not allow for assessment of events with a latency longer than 12 months.

4.2. EFFECT OF EXCLUSION CRITERIA IN THE CLINICAL TRIAL DEVELOPMENT PLAN

Members of the ED population that have been less well studied are reflected in the current sildenafil (ED) SmPC (See Section 4.4 Special Warnings and Precautions for Use).

Exclusion Criteria Which Will Remain as Contraindications	
Criteria	**Implications for Target Population**
Subjects who have a known hypersensitivity to sildenafil (ED) or any component of the study medication; subjects who have had any previous treatment-related intolerable side effects to sildenafil (ED).	The incidence of hypersensitivity to sildenafil (ED) is not known but estimated to be low. Sildenafil (ED) is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
Subjects with significant cardiovascular disease in the last 3 months, including (severe) cardiac failure, stroke, myocardial infarction, or unstable angina.	Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. If sexual activity is deemed unadvisable by the physician, then sildenafil (ED) should not be used.
Subjects who are currently prescribed, taking, and/or likely to be treated with nitrates or nitric oxide donors in any form on either a regular or an intermittent basis.	Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil (ED) was shown to potentiate the hypotensive effects of nitrates. Its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.
Subjects with severe hepatic impairment, a known history of retinitis pigmentosa, or hypotension (BP<90/50 mm Hg).	The safety of sildenafil (ED) has not been studied and its use is contraindicated in patients with the following co-morbid conditions: severe hepatic impairment, hypotension (blood pressure <90/50 mm Hg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
Subjects who have loss of vision in 1 eye because of non-arteritic anterior ischaemic optic neuropathy (NAION),	Cases of NAION, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil (ED) and other PDE5 inhibitors, therefore sildenafil (ED) is contraindicated in patients with prior history of NAION

Exclusion Criteria Which are NOT Proposed to Remain as Contraindications		
Criteria	Reason for Being an Exclusion Criterion	Justification for not Being a Contraindication
Subjects with significant cardiovascular disease in the last 3 months, including cardiac failure, stroke, myocardial infarction, unstable angina and symptomatic or clinically significant cardiac arrhythmias	Sexual activity is associated with some degree of cardiac risk, and given the vasodilating properties of sildenafil (ED). It is recommended that physicians consider cardiovascular status of patients prior to initiating treatment for erectile dysfunction.	The treating physician should use his/her judgment of risk/benefit for individual patients. Special warnings and precautions are recommended for patients with a history of cardiovascular disease in Section 4.4 of the SmPC under the subheading Cardiovascular Risk factors.
Subjects who have been treated with more than 6 doses of any other phosphodiesterase type 5 (PDE-5) inhibitor such as vardenafil or tadalafil for erectile dysfunction	Other PDE-5-type inhibitors were excluded from use in clinical studies to avoid an accumulation effect and to ensure that the efficacy assessment was not confounded by the effects of these agents.	The treating physician should use his/her judgment of risk/benefit for individual patients. No data are available regarding the use of sildenafil (ED) with other PDE-5 inhibitors. This issue is addressed in Section 4.4 of the SmPC under the subheading Concomitant use with other treatments for erectile dysfunction.
Subjects currently taking any other commercially available drug or non-drug treatments for erectile dysfunction (i.e., intraurethral agents, prostheses, injection therapy, topical applications, herbal or alternative medications, or vacuum-assisted erection devices. Such treatments must be terminated at or before the screening visit and must not be taken at any time during the study	Other concomitant ED treatments were excluded from use in clinical studies to avoid an accumulation effect and to ensure that the efficacy assessment was not confounded by the effects of these agents.	The treating physician should use his/her judgment of risk/benefit for individual patients. No data are available regarding the use of sildenafil (ED) with other PDE-5 inhibitors. This issue is addressed in Section 4.4 of the SmPC under the subheading Concomitant use with other treatments for erectile dysfunction.
Subjects who are currently being treated with or are likely to be prescribed alpha blocker medications	Co-administration of sildenafil (ED) and alpha blocker medication may lead to symptomatic hypotension in a few susceptible individuals	The treating physician should use his/her judgment of risk/benefit for individual patients. This issue is addressed in Section 4.4 of the SmPC under the subheading Concomitant use with alpha-blockers). Caution is advised when sildenafil (ED) is administered to patients taking an alpha-blocker

Exclusion Criteria Which are NOT Proposed to Remain as Contraindications		
Criteria	Reason for Being an Exclusion Criterion	Justification for not Being a Contraindication
Subjects who are receiving concomitant treatment with potent CYP3A4 inhibitors such as ritonavir, saquinavir, ketoconazole, itraconazole, erythromycin and cimetidine	Sildenafil (ED) metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil (ED) clearance. .	The treating physician should use his/her judgment of risk/benefit for individual patients. Use of sildenafil (ED) with CYP3A4 inhibitors is described in Section 4.2 of the SmPC. Caution is advised when using sildenafil (ED) with ritonavir in section 4.4 of SmPC. This issue also is addressed in Section 4.5 of the SmPC under the subheading of Effects of other medicinal products on sildenafil (ED) interaction with CYP3A4 inhibitors.
Subjects with severe renal impairment	Sildenafil (ED) clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min).	The treating physician should use his/her judgment of risk/benefit for individual patients. Starting dose of 25 mg is recommended for patients with severe renal impairment in Section 4.2 of the SmPC.
Subjects with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption,	The film coating of sildenafil (ED) tables contains lactose.	The treating physician should use his/her judgment of risk/benefit for individual patients. Section 4.4 of the SmPC states that the film coating of the tablet contains lactose and that sildenafil (ED) should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

The interventional clinical trial program has now completed. No further sponsored studies are planned at the current time. Therefore, there is no plan to assess in the clinical setting the patient populations meeting the exclusion criteria listed above, that will therefore remain as contraindications in the sildenafil (ED) SmPC.

4.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Children	Paediatric patients were not studied in the sildenafil (ED) clinical program. Sildenafil (ED) is not indicated for patients <18 years of age. No paediatric investigational program for sildenafil (ED) is planned.
Elderly	There were 3,537 patient ≥65 years of age enrolled in the clinical programme with the total exposure duration of 2362 years. Cumulative analysis of double-blind studies confirmed that sildenafil (ED) is well tolerated in men with erectile dysfunction (ED) overall and in those aged ≥65 years and ≥75 years. No dosage adjustment is required in elderly patients (≥65 years of age).
Pregnant or Breast-Feeding Women	Pregnant or nursing women have not been studied in the development program. Sildenafil (ED) is not indicated for use by women.
Patients with Hepatic Impairment	In healthy volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B). Sildenafil (ED) clearance was reduced; therefore dose adjustment should be considered for patients with hepatic insufficiencies. Sildenafil (ED) has not been studied in patients with severe hepatic impairment (Child-Pugh C) and therefore is contraindicated.
Patients with Renal Impairment	No dose adjustment is recommended for patients with mild to moderate renal impairment (creatinine clearance 30-80 mL/min). In patients with severe renal impairment (creatinine clearance <30 mL/min) sildenafil (ED) clearance is reduced and a 25-mg dose should be considered.
Patients with Other Relevant Co-morbidity	Though subjects with significant cardiovascular disease in the last 3 months were not studied in clinical program, based on the cumulative analysis of the double-blind studies there is no causal link between sildenafil (ED) and cardiovascular events. However, since sexual activity is associated with some degree of cardiac risk and given the vasodilating properties of sildenafil (ED), it is recommended that physicians consider cardiovascular status of patients prior to initiating treatment for erectile dysfunction. Though subjects who are treated with or are likely to be prescribed alpha blocker medications were excluded from clinical program, co-administration of sildenafil (ED) with alpha-blocker may lead to postural hypotension. Therefore caution is advised when sildenafil (ED) is administered to patients taking an alpha blocker and it is recommended that patients are haemomodynamically stable on alpha-blocker prior to starting sildenafil (ED).
Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population	Viagra is indicated for male patients with ED and does not have limitations on the degree of the disease severity.

Subpopulations Carrying Known and Relevant Polymorphisms	No studies have been carried out to assess populations with polymorphisms that could affect treatment with sildenafil (ED).
Patients of Different Racial and/or Ethnic Origin	Different ethnic groups were included in the clinical study program. In the double-blind studies, the majority of recruited subjects on sildenafil (ED) (6081) was Caucasian. Other ethnic groups included blacks (619), orientals (1274), American Indians (427), and Latin Americans (292) Information about race was missing for 877 subjects. Efficacy and safety of sildenafil (ED) was investigated in Black Americans (study A1481006); in Chinese men (A148-803) , in men with ED in the Republic of South Korea (SDN-K-98-001), in men with ED in Latin America (SDN-LA-97-001; SDN-LA-97-003; SDN-LA-97-004), and in men with ED in Asia (SDN-NY-96-002; SDN-NY-96-003; SDN-NY-96-006). No notable differences were seen in safety or efficacy in the populations studied.

4.4. CONCLUSIONS ON THE POPULATIONS NOT STUDIED AND OTHER LIMITATIONS OF THE CLINICAL TRIAL DEVELOPMENT PROGRAMME

Safety concerns due to limited use in patients with severe hepatic impairment are reflected in the label as contraindications for patients with severe hepatic impairment. Sildenafil (ED) was not studied in women and children because it is not indicated for use in these populations. No new safety concerns have been identified from the clinical trial and post-marketing databases. Currently, there are no further interventional studies planned.

Missing Information and Additional Safety Concerns Due to Limitations of the Clinical Trial Programme		**Outstanding Concern?**
Safety Concern	**Comment**	**Yes/No**
Severe hepatic impairment	Patients with severe hepatic impairment were excluded from clinical trials. Sildenafil (ED) use has been studied in otherwise healthy volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B), and in these subjects Sildenafil (ED) clearance was reduced.	Yes

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

5.1. ACTION TAKEN BY REGULATORY AUTHORITIES AND/OR MARKETING AUTHORISATION HOLDERS FOR SAFETY REASONS

Since the first marketing authorisation of sildenafil (ED) for male patients with erectile dysfunction in 1998, the following regulatory actions have been taken for safety reasons either by the Health Authority or by the Marketing Authorisation Holder.

Regulatory Actions Taken for Safety Reasons Since Last Risk Management Plan			
Safety Concern – NAION			
Country	**Action Taken**	**Comment**	**Date(s)**
Canada	On 23 May 2013 Pfizer submitted proposed language to modify existing Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) information in the **WARNINGS AND PRECAUTIONS, UNDER PART I (HEALTH PROFESSIONAL INFORMATION)** and in **PART III (CONSUMER INFORMATION)** of the sildenafil (ED) Product Monograph to reflect the results from Study A1481259, entitled "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential 'Trigger Factor' for Acute NAION". In addition to the updates Pfizer proposed, Health Canada requested that a contraindication is also added in patients with erectile dysfunction with previous episode of NAION.	Pfizer submitted global changes to sildenafil (ED) labeling to modify existing NAION information to reflect the results from Study A1481259. Regulatory Authority reviews are ongoing in several countries including the United States and Japan.	28 Aug 2013
Singapore	On 7 August 2013 Pfizer submitted proposed language to modify existing NAION information in the **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** section of the sildenafil (ED) labeling to reflect the results from Study A1481259, entitled "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential 'Trigger Factor' for Acute NAION". In addition to the updates Pfizer proposed, Health Sciences Authority, Singapore requested that a contraindication is also added in patients with erectile dysfunction with previous episode of NAION.	--	23 Aug 2013

Regulatory Actions Taken for Safety Reasons Since Last Risk Management Plan			
Safety Concern – NAION			
Country	**Action Taken**	**Comment**	**Date(s)**
EU	On 07 May 2013 Pfizer submitted proposed language to modify existing Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) information in Section 4.4 Special warnings and precautions for use of the sildenafil (ED) SPC to reflect the results from Study A1481259, entitled "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential 'Trigger Factor' for Acute NAION".	--	25 Jul 2013
New Zealand	On 4 June 2013 Pfizer submitted proposed language to modify existing NAION information in the **WARNINGS and PRECAUTIONS** and **ADVERSE EFFECTS** sections of the sildenafil (ED) labeling to reflect the results from Study A1481259, entitled "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential 'Trigger Factor' for Acute NAION".	This was considered a self-assessable change	4 Jun 2013
Australia	On 14 May 2013 Pfizer submitted proposed language to modify existing NAION information in the **PRECAUTIONS** and **ADVERSE EFFECTS** sections of the sildenafil (ED) labeling to reflect the results from Study A1481259, entitled "Case-Crossover Study of PDE5 Inhibitor Exposure as a Potential 'Trigger Factor' for Acute NAION".	--	22 May 2013
Safety Concern – Patients who are currently taking amiodarone hydrochloride			
Japan	Pfizer Japan requested Pharmaceuticals and Medical Devices Agency (PMDA) to add a new **CONTRAINDICATION** for patients who are currently taking amiodarone hydrochloride because patients taking sildenafil (ED) was listed as a contraindication in the amiodarone hydrochloride JPI.	--	Jan 2008
Safety Concern – Hearing Loss			
United States	Updated **PRECAUTIONS, ADVERSE REACTIONS/CLINICAL TRIALS/SPECIAL SENSES, POST-MARKETING EXPERIENCE/SPECIAL SENSES** sections of PI and **POSSIBLE SIDE EFFECTS** section of PPI to address the potential for sudden decrease or loss of hearing.	--	18 Oct 2007

Cumulative Regulatory Actions Taken for Safety Reasons			
Safety Concern – Cardiovascular Events			
Country	**Action Taken**	**Comment**	**Date(s)**
United States	Added the following information under **WARNINGS**: Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including sildenafil (ED) - those with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.		19 Sep 2002
Sudan	Under the section **CONTRAINDICATIONS** the following *italicized* text was added: *Serious cardiovascular events, including myocardial infarction, angina pectoris intermediate syndrome, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of VIAGRA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.*		10 Jul 2000

Cumulative Regulatory Actions Taken for Safety Reasons			
Safety Concern – Cardiovascular Events			
United States	Updated **WARNINGS** to add: • Potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease • That sildenafil (ED) has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers • Statement that there is no controlled clinical data on the safety or efficacy of sildenafil (ED) in the following groups and if prescribed, this should be done with caution: Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months; Patients with resting hypotension or hypertension; Patients with cardiac failure or coronary artery disease causing unstable angina; Patients with retinitis pigmentosa A Dear Healthcare Professional Letter was issued to advise of these labeling updates		24 Nov 1998
Safety Concern – NAION			
EU	On 17 Feb 2006 a Type II variation was submitted to the EMA relating to update the SPC, Annex II, labelling and Package Leaflet. This variation related to an update of the SPC section 4.3 (**CONTRAINDICATIONS**) to include a statement that PDE5 inhibitors are contraindicated in patients with a previous episode of Non-arteritic anterior ischemic optic neuropathy (NAION). Sections 4.4 and 4.8 of the Summary of Product Characteristics were also amended in order to include information with regard to non-arteritic anterior ischemic optic neuropathy (NAION). The PL was updated accordingly. In addition, the contact details of the local representatives in Poland and Sweden have been amended and the MAH took the opportunity to update the Product Information in accordance to QRD template version 7.		8 Jun 2006

Cumulative Regulatory Actions Taken for Safety Reasons			
Safety Concern – NAION			
EU	On the 8 July 2005 a Type II variation was submitted to the EMA relating to update the SPC, labelling and Package Leaflet. This variation related to an update of the SPC section 4.4 (**SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**) to include a warning stating that PDE5 inhibitors are not recommended in patients with a previous episode of Non-arteritic anterior ischemic optic neuropathy (NAION). Section 4.8 (**UNDESIRABLE EFFECTS**) was also amended to add Non-arteritic anterior ischemic optic neuropathy (NAION) and visual field defect and retinal vascular occlusion at the request of the CHMP. The Package Leaflet (PL) was also amended accordingly.		15 Nov 2005
United States	Addition of information to the **PRECAUTIONS, INFORMATION FOR PATIENTS** and **POST-MARKETING EXPERIENCE/SPECIAL SENSES SECTIONS** in regard to postmarketing reports of vision loss due to non-arteritic anterior ischemic optic neuropathy (NAION) in men who had taken PDE5 inhibitors, including sildenafil (ED). A Dear Healthcare Professional letter was also issued to advise of this label update.		8 Jul 2005
Safety Concern – Interaction with alpha-blockers			
United States	Updated **PRECAUTIONS** for specific considerations when using sildenafil (ED) with alpha blockers		26 Jun 2006
EU	On the 6 January 2005 a Type II variation was submitted to the EMA relating to update the SPC, labelling and Package Leaflet. This Variation related to changes to the Summary of Product Characteristics (SPC) sections 4.2 (**POSOLOGY AND METHOD OF ADMINISTRATION**), 4.4 (**SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**) and 4.5 (**INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**) to include information on the potential interaction between sildenafil (ED) and alpha blockers following a re-evaluation of the original data and the completion of a sildenafil-doxazosin interaction clinical trial study. Corresponding changes have been introduced in section 2 of the Package Leaflet (PL).		27 Apr 2005

Cumulative Regulatory Actions Taken for Safety Reasons			
Safety Concern - Nitrates			
United States	With respect to nitrate use, the **CONTRAINDICATIONS** section was clarified and enhanced pharmacokinetic information was added.		24 Nov 1998
Safety concern – Co-administration with ritonavir			
Sudan	Under the section **CONTRAINDICATIONS** the following *italicized* text was added: *Co-administration of sildenafil with ritonavir is not advised (see Section 4.5 Interaction with other medicinal products and other forms of interaction).* Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro …		10 Jul 2000
Safety concern - Priapism			
United States	Addition of the following **WARNING**: *Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA.* *In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.* A Dear Healthcare Professional Letter was also issued to advise of this labeling update		24 Nov 1998
Safety concern: Systemic vasodilatory effects			
Japan	Under the section **SPECIAL WARNINGS/PRECAUTIONS FOR USE** the following was added: *** (10) Patients with multiple system atrophy (Shy-Drager syndrome, etc). [The vasodilator action of Viagra could worsen the hypotension caused by the underlying disease(s).]*		21 Sept 2000
Safety Concern: Use with other PDE5 inhibitors			
United States	Updated **PRECAUTIONS/INFORMATION FOR PATIENTS** regarding use with other PDE5 inhibitors including Revatio.		11 Jan 2010

Cumulative Regulatory Actions Taken for Safety Reasons			
Safety Concern: Patients with Sickle Cell Disease			
United States	Updated information on *sickle cell disease* under **WARNINGS** regarding lack of controlled clinical data on safety or efficacy in patients with sickle cell disease.		31 Jan 2011

5.2. NON-STUDY POST-AUTHORISATION EXPOSURE

5.2.1. Method Used to Calculate Exposure

The worldwide exposure estimate is based on audited pharmacy wholesaler sales data for sildenafil (ED) from July 2001 through June 2013 provided by IMS Health Prescribing Insights.

It should be noted that the above calculation of patient-years provides only a gross approximation of patient exposure, and should be used with caution when attempting a determination of estimates of reporting rates. The following factors hamper an accurate calculation of the total number of patients exposed to sildenafil (ED):

- The duration of treatment with sildenafil (ED) may vary extensively from patient to patient; in addition, use is intermittent, on a PRN basis.
- The lack of adherence, as not all patients comply with their prescribed dosage regimen;
- As the patient exposure calculation is based on sales data, it does not necessarily correlate with the amount of sildenafil (ED) administered.

5.2.2. Exposure

The following data (Table 1, Table 2, and Table 3) refer to the estimated number of tablets of sildenafil (ED) that have been sold worldwide from July 2001 through June 2013. A dose of sildenafil (ED) is assumed to be one 25 mg, 50 mg, or 100 mg tablet. The number of doses therefore corresponds to the number of tablets sold.

Table 1. Distribution of Sildenafil (ED) Standard Units (Tablets) by European Union Country

Country	Total (All Brand Names of Sildenafil for ED) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
Austria R&H	**8,484.7**	**8,466.7**
100 mg	5,068.5	5,055.8
50 mg	3,259.5	3,254.5
25 mg	156.7	156.4
Belgium R&H	**12,396.1**	**12,371.7**
100 mg	8,787.5	8,766.4
50 mg	3,251.1	3,248.2

Country	Total (All Brand Names of Sildenafil for ED) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
25 mg	357.5	357.1
Bulgaria R&H	**2,111.7**	**2,111.7**
100 mg	1,156.3	1,156.3
50 mg	688.1	688.1
25 mg	267.3	267.3
Croatia R&H	**1078.9**	**1078.9**
100 mg	465.8	465.8
50 mg	448.2	448.2
25 mg	164.9	164.9
Czech R&H	**4,340.1**	**4,340.1**
100 mg	3,211.8	3,211.8
50 mg	1,070.9	1,070.9
25 mg	57.4	57.4
Denmark Combined	**5,548.8**	**5,526.9**
50 mg	2,778.4	2,773.7
100 mg	2,338.7	2,321.6
25 mg	431.7	431.6
Finland R&H	**12,935**	**11,502.4**
100 mg	7,626.5	6,452.0
50 mg	4,982.8	4,728.5
25 mg	325.7	321.9
France R&H	**36,198.3**	**36,195.1**
50 mg	18,934.0	18,933.0
100 mg	14,324.6	14,322.4
25 mg	2,939.7	2,939.7
Germany P&H	**53,901.5**	**53,671.4**
100 mg	39,000.5	38,826.9
50 mg	12,972.9	12,919.9
25 mg	1,928.1	1,924.6
Greece Retail	**20,458**	**20,458**
50 mg	9,661.6	9,661.6
100 mg	7,684.3	7,684.3
25 mg	3,112.1	3,112.1
Hungary R&H	**6,886.8**	**6,365.6**
100 mg	5,005.7	4,513.6
50 mg	1,647.6	1,622.4
25 mg	233.5	229.6
Ireland R&H	**8,296.1**	**8,295.4**
100 mg	4,289.5	4,289.1
50 mg	3,577.9	3,577.6
25 mg	428.7	428.7
Italy R&H&DPC	**74,187.1**	**74,010.3**
50 mg	41,869.9	41,774.2
100 mg	24,688.4	24,613.4
25 mg	7,628.8	7,622.7
Latvia Retail	**748.7**	**748.7**
100 mg	582.1	582.1
50 mg	166.5	166.5
25 mg	0.1	0.1

Country	Total (All Brand Names of Sildenafil for ED) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
Luxembourg Retail	**986.2**	**985.2**
100 mg	686.7	685.9
50 mg	271.8	271.6
25 mg	27.7	27.7
Netherlands R&H	**10,749.9**	**10,749.9**
100 mg	5,525.3	5,525.3
50 mg	4,382.1	4,382.1
25 mg	842.5	842.5
Norway R&H	**9,924.9**	**9,924.9**
100 mg	5,596.8	5,596.8
50 mg	3,801.5	3,801.5
25 mg	526.6	526.6
Poland R&H	**5,215.8**	**5,215.8**
100 mg	3,394.3	3,394.3
50 mg	1,490.2	1,490.2
25 mg	331.3	331.3
Portugal R&H	**9,057.4**	**9,057.4**
50 mg	5,469.9	5,469.9
100 mg	2,354.7	2,354.7
25 mg	1,232.8	1,232.8
Slovenia Combined	**1618**	**1618**
100 mg	859.5	859.5
50 mg	648.8	648.8
25 mg	109.7	109.7
Spain R&H	**43,994.3**	**43,994.3**
50 mg	23,642.8	23,642.8
100 mg	16,568.1	16,568.1
25 mg	3,783.4	3,783.4
Sweden Combined	**16,351**	**16,350.5**
50 mg	8,791.0	8,790.9
100 mg	6,522.2	6,521.8
25 mg	1,037.8	1,037.8
UK R&H	140,453	140,453
100 mg	76,060.9	76,060.9
50 mg	53,887.1	53,887.1
25 mg	10,505.0	10,505.0
Total	**485,922.3**	**483,491.9**

Abbreviations: DPC=consumption of pharmaceutical products dispensed by regional or local health authorities directly to patients; ED=erectile dysfunctile; H=hospital; R=retail.

Table 2. Distribution of Sildenafil (ED) Standard Units (Tablets) by Non-European Union Country

Country	Total (All Brand Names) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
Algeria Retail	**6,056.3**	6,056.3
50 mg	5,445.2	5,445.2
100 mg	611.1	611.1
Argentina Retail	**1,890.2**	762.7
50 mg	1,570.3	762.7
100 mg	270.2	---
25 mg	49.7	---
Australia R&H	**31,241.2**	31,241.2
100 mg	26,308.6	26,308.6
50 mg	4,209.6	4,209.6
25 mg	723.0	723.0
Brazil R&NR	**100,831.9**	100,500.8
50 mg	88,565.4	88,234.3
25 mg	6,346.7	6,346.7
100 mg	5,919.8	5,919.8
Canada R&H	**72,177.3**	72,175.6
100 mg	57,452.2	57,450.6
50 mg	12,926.4	12,926.3
25 mg	1,798.7	1,798.7
C America Retail	**4,237.1**	4,237.1
100 mg	2,586.8	2,586.8
50 mg	1,650.3	1,650.3
Chile Retail	**1278.8**	1278.8
50 mg	799.7	799.7
100 mg	473.4	473.4
25 mg	5.7	5.7
China Hospital	**3,217.4**	3,217.4
100 mg	2,877.9	2,877.9
50 mg	339.5	339.5
25 mg	0.0	0.0
Colombia retail	**2,626.9**	2,626.9
50 mg	2,198.9	2,198.9
100 mg	428.0	428.0
Ecuador Retail	**1,548.1**	1,548.1
50 mg	1,427.1	1,427.1
100 mg	121.0	121.0
Egypt Retail	**15,688.5**	15,688.5
50 mg	15,688.5	15,688.5
Fr. W. Africa Retail	**870.6**	870.6
50 mg	796.0	796.0
100 mg	74.6	74.6
25 mg	0.0	0.0
Hong Kong Combined	**6,512.3**	6,512.3
100 mg	4,412.8	4,412.8
50 mg	2,041.6	2,041.6
25 mg	57.9	57.9

Country	Total (All Brand Names) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
India R&H	**1802.8**	1802.8
50 mg	986.9	986.9
100 mg	815.9	815.9
Indonesia Total Market	**5,062.8**	5,062.8
100 mg	3,887.1	3,887.1
50 mg	1,066.1	1,066.1
25 mg	109.6	109.6
Jordan Retail	**418.5**	418.5
50 mg	418.5	418.5
Kuwait Retail	**1,532.5**	1,532.5
50 mg	1,440.0	1,440.0
100 mg	92.5	92.5
Japan Combined	**65,671.1**	65,671.1
50 mg	58,340.6	58,340.6
25 mg	7,330.5	7,330.5
Korea R&H&C	**38,078.7**	38,018.6
100 mg	27,896.3	27,865.4
50 mg	10,102.5	10,073.3
25 mg	79.9	79.9
Lebanon Retail	**1,592.6**	1,592.6
50 mg	1,500.7	1,500.7
100 mg	91.9	91.9
Malaysia Combined & Gov	**8,091.7**	8,091.7
100 mg	6,281.1	6,281.1
50 mg	1,810.6	1,810.6
Mexico Retail & Non Retail	**53,810.7**	50,957.1
100 mg	35,163.3	33,058.5
50 mg	18,647.4	17,898.6
Morocco Retail	**4,877.7**	4,877.7
50 mg	3,228.6	3,228.6
100 mg	1,649.1	1,649.1
New Zealand R&H	**5,655.8**	3,807.8
100 mg	4,671.4	2,961.8
50 mg	816.3	689.7
25 mg	168.1	156.3
Peru Retail	**1,625.9**	1,625.9
50 mg	1,051.7	1,051.7
100 mg	539.3	539.3
25 mg	34.9	34.9
Russia R&H&DLO	**49,669.4**	49,669.4
100 mg	28,871.9	28,871.9
50 mg	17,531.3	17,531.3
25 mg	3,266.2	3,266.2
Singapore Combined & Gov	**5,119.7**	5,119.7
100 mg	4,020.5	4,020.5
50 mg	1,099.2	1,099.2
Switzerland R&H	**13,573.3**	13,498
50 mg	6,277.5	6,250.1
100 mg	5,966.0	5,922.4
25 mg	1,329.8	1,325.5
T urkey R&H	**41,780.6**	41,780.6

Country	Total (All Brand Names) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
100 mg	20,225.4	20,225.4
50 mg	18,492.1	18,492.1
25 mg	3,063.1	3,063.1
Philippines R&H	**2,288.1**	2,288.1
100 mg	1,051.0	1,051.0
50 mg	961.5	961.5
25 mg	275.6	275.6
Puerto Rico R&H	**5,483.6**	5,483.6
100 mg	4,192.8	4,192.8
50 mg	1,191.2	1,191.2
25 mg	99.6	99.6
Saudi Arabia Retail	**30,495.1**	30,495.1
50 mg	28,727.7	28,727.7
100 mg	1,508.9	1,508.9
25 mg	258.5	258.5
S Africa Tot Mkt&Hosp	**7,962.4**	7,854.5
100 mg	4,092.8	4,026.9
50 mg	3,187.5	3,145.5
25 mg	682.1	682.1
Taiwan R&H	**24,878.3**	24,878.3
100 mg	23,076.8	23,076.8
50 mg	1,799.6	1,799.6
25 mg	1.9	1.9
Thailand R&H	**901**	901
50 mg	475.5	475.5
100 mg	425.5	425.5
Tunisia Retail	**487.7**	487.7
50 mg	233.4	233.4
100 mg	191.1	191.1
25 mg	63.2	63.2
UAE Retail	**5,867**	5,867
50 mg	5,271.6	5,271.6
100 mg	595.4	595.4
Uruguay R&Mutuales	**526.4**	526.4
50 mg	320.4	320.4
100 mg	206.0	206.0
USA Total	**1,110,524.1**	1,110,524.1
100 mg	795,113.1	795,113.1
50 mg	297,420.0	297,420.0
25 mg	17,991.0	17,991.0
Venezuela Retail	**9,454.9**	9,454.9
50 mg	8,962.1	8,962.1
100 mg	492.8	492.8
Total	**1,745,409**	1,739,003.8

Abbreviations: C=clinics; DLO=product volume through the Russian government reimbursement programme; ED=erectile dysfunctile; Gov=government; H=hospital; Hosp=hospital; mkt=marketed; NR=non-retail; R=retail; tot=total.

Table 3. Distribution of Sildenafil (ED) Standard Units (Tablets) by European and Non-European Union Countries

Country	Total (All Brand Names) Standard Units (Thousands)	Total (Viagra) Standard Units (Thousands)
European Union Countries	**485,922.3**	**483,491.9**
Non-European Union Countries	**1,745,409**	**1,739,003.8**
Totals	**2,231,331.3**	**2,222,495.7**

Exposure data by age and gender presented in Table 4 is based on information provided by IMS Health Prescribing Insights 2010 through June 2013. Reasons for use of sildenafil (ED) in women and paediatric patients are not known. Revatio (sildenafil (PAH) is indicated for the treatment of pulmonary hypertension; it is possible that this accounts for some of the use of sildenafil (ED) in women and paediatric patients.

Table 4. Number of Prescriptions by Age and Gender (2010 through June 2013)

Age Group	Total (Thousands)	Female (Thousands)[a]	Male (Thousands)	Patient Sex Unspecified (Thousands)
17 and below	9	2	7	---
18 - 30	185	3	182	---
31 - 50	3,052	20	3,033	---
51 - 64	5,125	13	5,111	1
65 - 74	2,903	9	2,893	---
75 and above	799	6	793	---
Age Unspecified	262	---	257	6
Total	**12,335**	**53**	**12,275**	**7**

a. Indication unknown

5.3. POST-AUTHORISATION USE IN POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Paediatric Use		
Estimated Use	**Number (Thousands)**	**Comment on Any Variation in Benefit or Risk From Overall Target Population**
• Pre-term new-borns • Neonates (birth to 27 days) • Infants and toddlers (1 month to 23 months) • Children (2 years to e.g. 11 years) • Adolescents (e.g. 12 years to 18 years)	Use of sildenafil (ED) among paediatric patients is small (9/12,335) based on prescription data.	Reasons for the paediatric use of sildenafil (ED) are not known. Revatio (sildenafil citrate) is indicated for the treatment of pulmonary hypertension in paediatric patients; it is possible that this accounts for most paediatric use of sildenafil (ED). Other possible uses are secondary pulmonary hypertension, patent ductus arteriosis, and atresia of the pulmonary artery. Because sildenafil (ED) is the same moiety as sildenafil (PAH), it is expected that the risk would be similar to that of patients with PAH who take a comparable dose of Revatio.
Data source	IMS Database	
Method of calculation	Based on written prescriptions	

Paediatric Use
ED=erectile dysfunction; SmPC=summary of product characteristics.

Elderly Use		
Estimated Use	**Number (Thousands)**	**Comment on Any Variation in Benefit or Risk From Overall Target Population**
• 65 - 74 years • 75 and above	2,903 799	No difference in benefit or risk.
Data source	IMS Database	
Method of calculation	Based on written prescriptions	

Pregnant or Breast Feeding Women		
Estimated Use	**Number**	**Comment on Any Variation in Benefit or Risk From Overall Target Population**
• Pregnant • Breast feeding	61 Not available	Sildenafil (ED) has not been studied extensively in women. There were approximately 61cases of pregnancy-related exposures to sildenafil (ED) in women. These cases represent situations in which the women were either specifically prescribed sildenafil (ED) or were indirectly exposed to the product during sexual activity with a partner taking sildenafil (ED). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryonal/foetal development. Studies in animals have shown toxicity with respect to postnatal development. It is not known whether sildenafil (ED) enters the breast milk.
Data source	PfAST data	
Method of calculation	Compilation of SQL database search results	

Abbreviations: PfAST=Pfizer Analytical and Statistical Tool; SQL=Standard Query Language.

Hepatic Impairment		
Estimated Use	**Number**	**Comment on Any Variation in Benefit or Risk From Overall Target Population**
• Mild • Moderate • Severe	300 (severity data not available)	Since sildenafil (ED) clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg. Adherence to this dosing guideline should reduce the risk to patients with hepatic impairment
Data source	PfAST data	
Method of calculation	Compilation of SQL database search results	

Abbreviations: PfAST=Pfizer Analytical and Statistical Tool; SQL=Standard Query Language.

Renal Impairment		
Estimated Use	**Number**	**Comment on Any Variation in Benefit or Risk From Overall Target Population**
• Mild • Moderate • Severe	139 (severity data not available)	The dosing recommendations described in 'Use in adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 mL/min). Since sildenafil ED) clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg. Adherence to this dosing guidline should reduce the risk to patients with renal impairment.
Data source	PfAST data	
Method of calculation	Compilation of SQL database search results	

Abbreviations: PfAST=Pfizer Analytical and Statistical Tool; SQL=Standard Query Language.

5.4. POST-AUTHORISATION OFF-LABEL USE

5.4.1. POTENTIAL FOR OFF LABEL USE

A total of 861 cases[a] of off-label use of sildenafil (ED) were identified as of 30 Jun 2013. The majority of the 861 cases of off-label use have been related to drug use for unapproved indications such as treatment of premature ejaculation, libido decreased, penis disorder, prostatectomy, cardiovascular disorder, prostate operation, sexual activity increased, prostatic disorder, loss of libido, therapeutic procedure, and anorgasmia.

5.4.1.1. Off-label use in women

The MAH has clinical safety data of sildenafil (ED) use in women from a number of investigational studies for the indication of female sexual arousal disorder (FSAD). As of 29 June 2004, 1351 female subjects had received sildenafil (ED) in the dose range 10 to 100 mg. Ninety nine subjects received a single dose of sildenafil (ED) and 1252 subjects received multiple doses of sildenafil (ED) in the dose range 5 mg to 100 mg. In clinical studies of women with FSAD to date, the adverse event profile has been broadly similar to that of men, with adverse events (headache, flushing, dyspepsia, rhinitis, and visual disturbance) being largely mild to moderate, transient in nature, and associated with a low rate of discontinuation.

Eleven (11) cases reporting pregnancy originated from literature reports from the Japanese Society of Fertility and Sterility describing females with histories of conception difficulties who were administered 50 mg vaginal suppositories of sildenafil (ED) for In Vitro Fertilization (IVF) and Embryo Transfer (ET) and became pregnant Pregnancy outcomes

[a] Total does not include cases that coded to the MedDRA preferred terms, Product used for an Ill-defined disorder (14,869 cases), Unknown indication (411 cases), and Off-label use (31 cases).

were not provided in any of the cases. More recently, high implantation and on-going pregnancy rates were achieved after treatment with sildenafil (ED) in a cohort of 105 women with poor prognosis for success.[1]

While it confirmed the safety of the drug in females, this clinical program did not generate data that would unequivocally support the efficacy of sildenafil (ED) in the treatment of women with FSAD and was terminated.

5.5. EPIDEMIOLOGICAL STUDY EXPOSURE

The exposure in epidemiological studies is summarised in the table below.

Study Title and Study Type (e.g. Cohort or Case/Control)	**Objectives**	**Population Studied (Data Source and Country)**	**Duration (Study Period)**	**Number of Persons (in Each Group or of Cases and Controls) and Person Time (if Appropriate)**	**Comment**
Prescription Event Monitoring Study (Phase I); Cohort study[2]	A population-based study intended to measure the occurrence of selected short-term cardiovascular events in patients prescribed sildenafil (ED)	Individuals identified from National Health Service prescriptions in England during Sept 1998 – Mar 1999; data on cardiovascular events obtained via physician questionnaire	Average follow-up time was approximately 6 months	5,601 individuals prescribed sildenafil (ED) with complete questionnaire information were analyzed.	--
Prescription Event Monitoring Study (Phase II); Cohort study[3]	A population-based study intended to measure the occurrence of safety outcomes in patients prescribed sildenafil (ED)	Individuals identified from National Health Service prescriptions in England during Apr – Aug 1999; data on cardiovascular events obtained via physician questionnaire	Average follow-up time was approximately 18 months	22,473 individuals prescribed sildenafil (ED) with complete questionnaire information were analyzed.	--

Study Title and Study Type (e.g. Cohort or Case/Control)	Objectives	Population Studied (Data Source and Country)	Duration (Study Period)	Number of Persons (in Each Group or of Cases and Controls) and Person Time (if Appropriate)	Comment
International Men's Health Study; Cohort study[4]	A prospective cohort study designed to assess the incidence of serious cardiovascular disease (CVD) events [ie, myocardial infarction (MI) and stroke] and all-cause mortality in men with erectile dysfunction (ED) who received prescriptions for sildenafil (ED)	Men with ED who received a prescription for sildenafil (ED) in Germany, France, Spain, or Sweden during 2001-2003	Average follow-up time was approximately 9.2 months	3,813 men with ED prescribed sildenafil (ED) with complete baseline questionnaire information were analyzed (representing 2,935 person-years of follow-up)	--

References

1 Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. *Fertil Steril* 2002; May; 79(5): 1257-8.

2 Shakir SA, Wilton LV, Boshier A, et al. Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in England. *BMJ* 2001; 322: 651-2.

3 Boshier A, Pambakian N, Shakir SAW. A case of nonarteritic ischaemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; 40: 422-3.

4 Mittleman MA, Maclure M, Lewis MA, et al. Cardiovascular outcomes among sildenafil users: results of the International Men's Health Study. *Int J Clin Pract* 2008; 62:367-73.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

6.1. POTENTIAL FOR HARM FROM OVERDOSE

Sildenafil (ED) was studied up to 800 mg in single-dose volunteer studies during which adverse reactions were similar to those seen at lower doses, but the frequency and severity of adverse events increased. Doses of 200 mg increased the frequency of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision). Overall, at sildenafil (ED) doses studied that are higher than the maximum approved sildenafil (ED) dose for the indication of erectile dysfunction (ED), the frequency of visual adverse events increased with dose; however, there was no clear relationship between dose and maximum decreases in blood pressure. Experience from post-marketing data in which 1,100 cases of overdose have been reported cumulatively through 30 Jun 2013 does suggest there is a potential for overdose, but ongoing review of the data has not identified any notable safety concerns. In addition, experience from clinical trials with sildenafil was evaluated for the treatment of PAH in adults and has shown that sildenafil administered daily as doses of 120mg (40 mg TID) and 240mg (80mg TID) is considered safe, with the adverse event profile generally consistent with that of lower doses. Additionally, there were no clinically significant changes in electrocardiograms.

6.2. POTENTIAL FOR TRANSMISSION OF INFECTIOUS AGENTS

6.2.1. Suspected transmission of any infectious agent via sildenafil (ED) arising as a quality defect

None of the materials used in the manufacture or processing of sildenafil (ED) tablets is of animal and/or human origin. All excipients used in the tablet core formulation are of vegetable or synthetic origin. The lactose used in the film-coat formulation is produced from healthy animals in the same condition as those used to collect milk for human consumption. This lactose has been prepared without the use of ruminant material, other than calf rennet. The BSE risk in pharmaceutical grade lactose is negligible (EMEA/CPMP/BWP/227/02).

In both sildenafil pre-clinical studies and ED and PAH clinical studies, sildenafil has not been associated with an increased risk of infection. No potential for the direct transmission of infectious agents has been identified.

6.2.2. Suspected transmission of any infectious agent via sexual activity in patients using sildenafil (ED) arising as a pharmacovigilance issue

Most of the epidemiological information on recreational use of phosphodiesterase-5 (PDE5) inhibitors has been reported in the human immunodeficiency virus (HIV) prevention and treatment literature. Several surveys were conducted in populations of patients with or at risk for sexually transmitted disease (STD) including HIV/acquired immunodeficiency syndrome. The authors could not however establish a direct connection between the use of sildenafil (ED) and STD and/or HIV transmission.[1,2]

6.3. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Sildenafil (ED) has no ingredients that can be used for the manufacturing of controlled or illicit substances. Sildenafil (ED) does not alter the level of consciousness, does not have any effects on behavioral inhibition or decision making. Therefore there is no potential use as a substance for the commission of sexual assault.

There is no evidence from preclinical studies or Phase I-IV clinical studies to suggest that sildenafil (ED) has the potential for abuse. There are no underlying pharmacological mechanisms, or neural or behavioural signs and symptoms that suggest that sildenafil (ED) would induce drug-seeking behaviour. There have been no reports of drug abuse or drug dependence associated with the use of sildenafil (ED) in clinical trials.

Inappropriate recreational use of sildenafil (ED) and other PDE5 inhibitors has been reported; and the MAH is aware that all PDE5 inhibitors including sildenafil (ED) have been used by some consumers as recreational drugs shortly after their introduction in the market, first in the US and then in other countries including the EU, thus prompting an early debate about the safety of the illicit usage of these compounds.[3,4] However, most of these sildenafil (ED) consumers proved to be drug abusers, who reported having taken the compound simultaneously with illicit drugs, eg, cocaine (McLeod 2002), cannabis, methylenedioxymethamphetamine, amyl nitrite, and γ-hydroxybutyric acid.[5,6,7,8,9,10]

PDE5 inhibitors may potentially be misused by certain patient populations for their expected effects on sexual performance as much as for their proven efficacy in ED.[2]

6.4. POTENTIAL FOR MEDICATION ERRORS

6.4.1. Description of Medication Errors During the Clinical Trial Programme

There were no reports of medication errors during the clinical trial programme.

6.4.2. Preventive Measures for the Final Product(s) Being Marketed

The 3 strengths of the product are adequately differentiated by imprinted markings and physical size dimensions. Sildenafil (ED) film-coated tablets are blue, with a rounded-diamond shape, and imprinted with "PFIZER" on one side and "VGR 25", "VGR 50", and "VGR 100" on the other side to denote dose strengths of 25, 50, and 100 mg, respectively. In addition, the tablets increase in size with dose strength, measuring 9, 11, and 14 mm for the 25, 50, and 100 mg dose strengths, respectively.

6.4.3. Effect of Device Failure

Not applicable.

6.4.4. Reports of Medication Errors with the Marketed Product(s)

There are 1,815 reported occurrences of medication errors since sildenafil (ED) was first marketed through 30 June 2013. The errors with the highest frequency of occurrence are: inappropriate dose of drug administered, medication error, drug maladministration, expired drug used, incorrect dose administered, circumstance or information capable of leading to medication error, drug misadministration, expired drug administered, accidental exposure to product, and extra dose administered.

Description of Error	MedDRA Preferred Term	Number of Reports
Other Physician/Prescribing /Dispensing Errors	Medication error	243
	Inappropriate dose of drug administered	209
	Circumstance or information capable of leading to medication error	205
	Drug maladministration	158
	Incorrect dose administered	119
	Drug misadministration	99
	Drug administration error	35
	Drug prescribing error	27
	Drug dispensing error	19
	Wrong dose administered	13
	Wrong drug administered	13
	Incorrect route of drug administration	9
	Wrong drug strength dispensed	8
	Drug dose prescribing error	6
	Drug administered to patient of inappropriate age	5
	Drug dose administration interval too short	5
	Underdose	5
	Inappropriate schedule of drug administration	4
	Wrong drug dispensed	4
	Wrong patient received medication	4
	Drug administered via inappropriate route	3
	Intercepted drug prescribing error	3
	Drug administered at inappropriate site	2
	Inappropriate preparation of medication	2
	Incorrect drug dosage form administered	2
	Intercepted medication error	2
	Wrong dosage form dispensed	2
	Wrong injection technique	2
	Wrong route of administration	2
	Accidental exposure while preparing drug for administration	1
	Administered drug to incorrect patient	1

Description of Error	MedDRA Preferred Term	Number of Reports
	Drug dosage form prescribing error	1
	Drug route prescribing error	1
	Drug schedule prescribing error	1
	Intercepted drug dispensing error	1
	Wrong drug strength selected	1
	Wrong route of administration dispensed	1
	Total	**1218**
Other patient Errors	Accidental exposure to product	77
	Extra dose administered	64
	Counterfeit drug administered	35
	Accidental drug intake by child	34
	Wrong technique in drug usage process	18
	Inadvertent exposure to drug	7
	Once daily dose taken more frequently	5
	Drug dose omission	4
	Insufficient dosage	2
	Drug dose administration interval too long	1
	Incorrect drug administration duration	1
	Total	**248**
Expired Medication	Expired drug used	196
	Expired drug administered	107
	Expired drug dispensed	18
	Total	**321**
Poor Quality/Packaging Issue	Poor quality drug administered	7
	Product label issue	6
	Drug label confusion	2
	Total	**15**
Tablet Splitting, Crushing, Chewing	Tablet split incorrectly	7
	Inappropriate chewing of medication	4
	Tablet crushed incorrectly	4
	Total	**15**
Total		**1817**
	Source: http://ecf.pfizer.com/sites/DRMT/AES_Request_Deliverables/Forms/AllItems.aspx?RootFolder=%2Fsites%2FDRMT%2FAES%5FRequest%5FDeliverables%2FRequest%5F2013%2D6613%2FOutput%2FActual	

6.5. POTENTIAL FOR OFF LABEL USE

As Sildenafil (ED) use is restricted to adult males, there does exist the potential for off-label use in paediatric patients and women. As emphasized in the SPC, sildenafil (ED) has not been studied in these patient populations and thus its use is not indicated in these populations. Sildenaflil is approved in another presentation (sildenafil [PAH]) for the treatment of pulmonary arterial hypertension in adults and children. There remains the possibility that sildenafil (ED) may be used in place of sildenafil (PAH).

6.6. . SPECIFIC PAEDIATRIC ISSUES

6.6.1. Issues Identified in Paediatric Investigation Plans

There is no paediatric investigation plan in place for sildenafil (ED) and there are no plans for a paediatric development programme with the product.

6.6.2. Potential for Paediatric Off-label Use

Although sildenafil (ED) is not indicated in individuals under 18 years of age, marketing data show some small use in paediatric patients (See RMP Part II, Module SV). Sildenafil (ED) is the same moiety as sildenafil (PAH), Revatio, which is indicated for the treatment of pulmonary hypertension in paediatric patients; it is possible that this could lead to use of sildenafil (ED) to treat PAH. Other potential off-label uses are secondary pulmonary hypertension, patent ductus arteriosis, and atresia of the pulmonary artery.

6.7. CONCLUSIONS

Safety Concerns From This Module	
Safety Concern	**Comment**
Important identified risks	None
Important potential risks	None.
Missing information	None.

References

1 Chu PL, McFarland W, Gibson S, et al. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr* 2003; 33: 191-3.

2 Smith KM and Romanelli F. Recreational use and misuse of phosphodiesterase 5 inhibitors. *J Am Pharm Assoc* 2005; 45: 63-75.

3 Bowersox NK. Evaluating sildenafil in a state Medicaid population. Presented at the American Society of Health-System Pharmacists Midyear Clinical Meeting 1999 ; Abstract P-296D. Cited in Smith 2005.

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PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

NON-ATMP VERSION

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

7.1. NEWLY IDENTIFIED SAFETY CONCERNS (SINCE THIS MODULE WAS LAST SUBMITTED)

Since the last RMP (version 3.1), the MAH has not identified any new safety concerns and no new already identified safety concern required a change in categorization from an important potential to an important identified risk. It should be noted that the new important potential risk of "Eye haemorrhage" has been added to the sildenafil (ED) RMP at the request of the European Medicines Agency (EMA). In June 2013, the Committee for Medicinal Products for Human Use (CHMP) provided its assessment of the Marketing Authorisation Holder (MAH)'s cumulative review of the topic of chorioretinopathy and eye haemorrhage and concluded that "*Due to the number of cases involving eye haemorrhage events and a plausible mechanism of action as described in the SmPC, the Viagra RMP should be updated to include eye haemorrhage events as Important Potential Risk subject to close monitoring.*"

7.2. RECENT STUDY REPORTS WITH IMPLICATIONS FOR SAFETY CONCERNS

Recently, an observational non-interventional, case-crossover study (A1481259) conducted to examine whether as-needed use of phosphodiesterase- 5 (PDE5) inhibitors, as a class (including sildenafil (ED), vardenafil, or tadalafil), triggers the onset of acute non-arteritic anterior ischaemic optic neuropathy (NAION) within a pharmacokinetically-defined time period (approximately 5 half-lives) following drug ingestion was completed with the final study report submitted to the EMA in April 2013. The primary analysis of "definite NAION" cases suggests an approximately 2-fold increased risk of NAION within 5 half-lives of PDE5 inhibitor use; given that the outcome is rare, the odds ratio may be interpreted as an estimate of the relative risk.

7.3. DETAILS OF IMPORTANT IDENTIFIED AND POTENTIAL RISKS FROM CLINICAL DEVELOPMENT AND POST-AUTHORISATION EXPERIENCE (INCLUDING NEWLY IDENTIFIED)

7.3.1. Important Identified Risk – Nitrate Interaction

In preclinical studies, in anaesthesised dogs, sildenafil was shown to potentiate nitroglycerin induced postural hypotension. A study (148-209) conducted in human volunteers to assess the effects of sildenafil (25 mg) on the haemodynamic responses to glyceryl trinitrate (GTN) using a tilt table under laboratory conditions showed that sildenafil potentiated the hypotensive effects of sublingual and intravenous GTN and with multiple daily dosing (Study 148-209). Following this Phase I study, use in patients on chronic nitrates was contraindicated in all sildenafil ED Phase II/III studies.

Identified Risk: Nitrate Interaction	
Frequency	Unknown
Seriousness and Outcomes	Unknown
Severity and Nature of Risk	Coadministration of sildenafil (ED) and nitrates in pre-clinical studies resulted in hypotension. The same risk is present in humans. There was no coadministration of nitrates during clinical studies.
Background Incidence and Prevalence	Unknown
Risk Groups or Risk Factors	Patients taking nitric oxide donors or nitrates.
Potential Mechanisms	Nitric oxide induces the formation of intracellular cyclic guanosine monophosphate (cGMP) by guanylate cyclase.[1] Sildenafil selectively inhibits phosphodiesterase type 5 (PDE5) effectively blocking the degradation of cGMP. When nitrates and sildenafil were co-administered in preclinical studies larger but similarly transient effects on blood pressure were observed, consistent with their known effects on the NO-cGMP pathway.
Preventability	This interaction can be prevented by avoiding coadministration of sildenafil (ED) and nitrates. Nitrates are contraindicated in the sildenafil (ED) product label (see Section 4.3 of SmPC).
Impact on Individual Patient	Symptomatic hypotension could lead to risk of injury and risk of end organ damage including fatality.
Potential Public Health Impact of Safety Concern	The public health impact is an increase in the risk of hypotension in patient taking sildenafil (ED) concurrently with nitrates.
Evidence Source	Study A148-209.
MedDRA Terms	MedDRA HLT: Interactions MedDRA PTs: Labelled drug-drug interaction medication error, Labelled drug-food interaction medication error.

7.3.2. Important Potential Risk – Non-Arteritic Anterior Ischaemic Optic Neuropathy

Potential Risk: NAION	
Frequency with 95 % confidence interval (CI)	Clinical trials Ischaemic optic neuropathy (the Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT] including the low-level term [LLT] NAION) was not reported as an adverse events (AE) in any of the 23,182 subjects who were exposed to sildenafil (ED) in 136 double-blind and open label clinical studies of ED. However, several PTs possibly representing NAION were reported in 39 (0.2%) subjects (Amaurosis fugax, Blindness, Blindness transient, Blindness unilateral, Retinal vein thrombosis, Scotoma, and Visual acuity reduced).

<table>
<tr><th colspan="2">Potential Risk: NAION</th></tr>
<tr><td>Seriousness/outcomes</td><td>Among the 39 subjects in whom a NAION-related adverse event was reported, a serious adverse event was reported in 3 subjects.

<u>Post-marketing</u>

A prospective cohort study (the International Men's Health Study, IMHS) that enrolled 3813 men for 2935 patient-years of follow-up identified no NAION cases.[2] In another post-marketing (PM) study (The Sildenafil Prescription Event Monitoring study, PEM) that enrolled over 28,000 patients (5601patients for a mean follow-up of 6 months and 22,473 patients for a mean of almost 18 months), 1 case of NAION was reported, corresponding to unadjusted incidence of NAION of 2.8 per 100,000 person-years.[3,4,5]

Among the 1,671 cases reporting adverse events potentially related to NAION in the post-marketing safety database, the events outcomes were reported as follows: 7.2% recovered/resolved, 0.9% recovered/resolved with sequelae, 4.9% recovering/resolving, 29.5% not recovered/not resolved, and 58% unknown.</td></tr>
<tr><td>Severity and nature of risk</td><td><u>Clinical trials</u>

Of the 39 NAION-related adverse events reported, 64.1% (18/39) were considered mild, 20.5% (8/39) were considered moderate, and 15.4% (6/39) were considered severe.

<table>
<tr><th colspan="5">Incidence and Severity of Treatment-Emergent Adverse Events</th></tr>
<tr><td>MedDRA PT</td><td>N=39</td><td colspan="3">Severity</td></tr>
<tr><td></td><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>Amaurosis fugax</td><td>1</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Blindness</td><td>2</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Blindness transient</td><td>2</td><td>1</td><td>1</td><td>0</td></tr>
<tr><td>Blindness unilateral</td><td>1</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Retinal vein thrombosis</td><td>1</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Scotoma</td><td>4</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>Visual acuity reduced</td><td>25</td><td>18</td><td>4</td><td>3</td></tr>
<tr><td>Visual field defect</td><td>3</td><td>2</td><td>1</td><td>0</td></tr>
</table></td></tr>
</table>

Potential Risk: NAION	
Background incidence/prevalence	There are no published estimates of the incidence of NAION in patients with erectile dysfunction. Three studies have reported estimates for general populations within the US. A population-based study of two communities in the United States, the state of Missouri and the city of Los Angeles, CA, estimated that the US annualized incidence of NAION was 2.3 per 100,000 per year in those at least 50 years of age.[6] Johnson also found that both genders had similar incidence rates and Caucasians were affected approximately 8 times more often than African-Americans or Hispanics. They estimated the mean incidence rate for men aged 50 and older to be 2.52 (95% CI: 1.69-3.33) per 100,000 per year and 3.55 (95% CI: 2.30-4.81) per 100,000 per year in men aged 60 or older. A second study in Olmstead County, Minnesota found the unadjusted incidence rate of NAION in the US to be 10.3 per 100,000 per year (95% CI: 5.1-18.4) overall , and after adjustment for the age and sex distribution of the United States white population in 1990, the rate was 10.2 per 100,000 per year (95% CI: 6.5-15.6). In men, the crude annual incidence rate was estimated as 11.8 (95% CI 5.9-21.1) cases per 100,000 aged 50+ years.[7] Furthermore, the investigators estimated that there are approximately 5700 new cases every year in the US. The Ischemic Optic Neuropathy Decompression Trial estimated an annual incidence of 1500 to 6000 cases per year in the United States, which is similar to the incidence reported in the Olmstead County study.[8] In a more recent US study that involved analysis of Medicare claims data, NAION incidence was reported as 82 cases per 100,000.[9] However, the lack of claims code specific to NAION makes the case definition problematic, and this estimate may not be reliable. Little data are available on the incidence of NAION in the European Union (EU). Most EU population-based studies that examine the causes of blindness fail to identify optic neuropathy separately.[10,11,12,13,14] It is possible that NAION may be contained within an "other causes" category, but as most of these studies are small, they are limited in their ability to identify rare causes of blindness such as NAION. Only one study, the Rotterdam Study in the Netherlands, described "optic neuropathy" as a cause of blindness or visual impairment in residents aged 55 years or greater. [15] Unfortunately the subtypes of ischemic neuropathy (non-arteritic or arteritic) were not discussed, nor were the population incidence rates provided.
Risk groups or risk factors	Many of the risk factors of NAION are similar to those for erectile dysfunction, such as ischaemic heart disease, hypertension, hypercholesterolemia, diabetes, and increased age.[16,17,18,] Other potential risk factors for NAION are sleep apnea, hyperhomocystinemia, the presence of a disc-at-risk (ie, a crowded disc), cataract extraction and intraocular lens surgery, disorders of blood coagulation and specifically thrombotic tendency.[19,20] Patients who have experienced an episode of NAION in one eye are at higher risk of having it occur in the opposite eye, as well as those who have had cataract extraction, intraocular lens surgery, or who have a 'disc at risk'.
Potential mechanisms	There is no firmly established mechanistic explanation for the occurrence of NAION associated with the use of sildenafil (ED).

Potential Risk: NAION	
Preventability	Patients who have experienced blindness in one eye are at an increased risk for NAION should avoid sildenafil (ED) or use with caution.
Impact on individual patient	NAION leads to poor vision in one eye and in some cases may lead to second eye involvement. Vision acuity remains moderately impaired in most cases but in few cases may involve total loss of vision.
Potential public health impact of safety concern	A causal relationship has not been established between the use of PDE5 inhibitors and NAION. No public health impact is anticipated, based on the current data from the development program and post-marketing data.
Evidence source	Clinical trial and post-marketing data, published literature.
MedDRA terms (V 16.0)	MedDRA PTs: Amaurosis, Amaurosis fugax, Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Optic nerve disorder, Optic nerve infarction, Optic neuropathy, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Retinal infarction, Retinal ischaemia, Retinal vascular occlusion, Retinal vascular thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Scotoma, Sudden visual loss, Visual acuity reduced, and Visual field defect.

7.3.3. Important Potential Risk – Sudden Hearing Loss

Potential Risk: Sudden Hearing Loss	
Frequency with 95 % CI	Clinical trials Among all subjects (N=23,182) exposed to sildenafil (ED) in 136 double-blind and open label clinical trials, a total of 11 hearing loss-related adverse events were reported in 11 (0.05%) subjects. Treatment emergent all-causality hearing loss-related adverse events reported in these 136 clinical trials were Deafness, Deafness permanent, Deafness unilateral, Hearing impaired, Hypoacusis.
Seriousness/outcomes	Clinical trials Among the 11 subjects in whom a hearing loss-related adverse event was reported, a serious adverse event was reported in 3 subjects. Post-marketing In the post-marketing safety database (from first authorization to 30 June 2013), there were 389 sildenafil (ED) cases which reported a hearing loss-related adverse event, representing 0.62% of the total 62,864 sildenafil (ED) cases in the database. The reported hearing loss-related adverse events are deafness, deafness bilateral, deafness neurosensory, deafness transitory, deafness unilateral, hearing impaired, hypoacusis, and sudden hearing loss. Among the 389 hearing loss-related adverse events in the post-marketing safety database, the event outcomes were reported as follows: 8.0% recovered/resolved, 5.7% recovering/resolving, 32.4% not recovered/not resolved, and 54% unknown.
Severity and nature of risk	Clinical trials Among the 11 hearing loss-related adverse events reported, 54.5% (6/11) were considered mild, 9.1% (2/11) were considered moderate, and 27.3% (3/11) were considered severe.

Incidence and Severity of Treatment-Emergent Adverse Events

MedDRA PT	N=11	Severity		
		Mild	Moderate	Severe
Deafness	3	2	0	1
Deafness permanent	1	0	0	1
Deafness unilateral	2	1	0	1
Hearing impaired	1	0	1	0
Hypoacusis	4	3	1	0

Potential Risk: Sudden Hearing Loss	
Background incidence/prevalence	No published studies that directly assess the occurrence of hearing loss among men with erectile dysfunction are available. Background estimates for the general population are described below. Hearing loss is the third most prevalent chronic condition in older Americans, and between 25-40% of the population aged ≥65 years is estimated to be hearing impaired.[21,22,23] Although prevalence rises with age, ranging from 40-66% in patients aged >75 years and more than 80% in patients >85 years, age-adjusted hearing loss is known to have increased significantly since the 1960s.[24,25] In the Epidemiology of Hearing Loss study, the overall 5-year incidence of hearing loss (based on hearing sensitivity measurements) was 21.4% among subjects aged 48 to 92 years; hearing loss occurred more often in men than in women (OR = 2.71, 95% CI = 2.04–3.59).[26] Sudden sensorineural hearing loss (SNHL) is characterized by loss of hearing occurring over a period of 3 days or less.[27,28] SNHL varies in severity, but has been defined as 30 decibels or more over at least 3 adjacent audiometric frequencies.[29] In a population-based study of California residents, Byl (1977) estimated the incidence of SNHL as 10.7 cases per 100,000.[30] Typically, the annual incidence of SNHL is described as 5 to 20 cases per 100,000, as first reported in a 1984 literature review.[31,32] In this review, Byl also notes that incidence generally increases with age but unlike age-related hearing loss, the incidence of SNHL is similar between men and women.
Risk groups or risk factors	None specifically identified. Elderly patients may represent a potential risk group, as it is well known that the prevalence of hearing loss rises with age, ranging from 40-66% in patients aged >75 years to more than 80% in patients >85 year.
Potential mechanisms	No biologically plausible mechanism for sildenafil (ED) inducing hearing loss has been identifed.
Preventability	Patients at risk for hearing loss should use sildenafil (ED) with caution.
Impact on individual patient	Loss of hearing can significantly impact a person's ability to communicate with others, and lead to a reduced quality of life.
Potential public health impact of safety concern	Based on the current data from the development program and post-marketing surveillance, the public health impact of this potential risk is not known.
Evidence source	Clinical trial and post-marketing data, published literature.
MedDRA terms	MedDRA PTs: Conductive deafness, Deafness, Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Hearing impaired, Hypoacusis, and Sudden hearing loss.

7.3.4. Important Potential Risk – Eye Haemorrhage

Potential Risk Eye Haemorrhage	
Frequency with 95 % CI	Clinical trials Among all subjects (N=23,182) exposed to sildenafil (ED) in 136 double-blind and open label clinical trials, a total of 24 Eye haemorrhage-related adverse events were reported in 24 (0.10%) subjects. Treatment emergent all-causality eye haemorrhage-related adverse events reported in these 136 clinical trials were Vitreous haemorrhage, Conjunctival haemorrhage, Scleral haemorrhage, Eye haemorrhage, Retinal aneurysm, Retinal haemorrhage, Retinal neovascularisation, Retinal vein thrombosis. Post-marketing In the post-marketing safety database (from first authorization to 30 June 2013), there were 442 sildenafil (ED) cases which reported eye-haemorrhage-related adverse events, representing 0.70% of the total 62,864 sildenafil (ED) cases in the database. The eye-haemorrhage-related adverse events were: Choroidal infarction, Choroidal neovasculatisation, Conjunctival haemorrhage, Eye haemorrhage, Hyphaema, Macular ischaemia, Ocular vascular disorder, Polyproidal choroidal vasculopathy, Retinal aneurysm, Retinal artery embolism, Retinal artery occlusion, Retinal artery spasm, Retinal artery thrombosis, Retinal haemorrhage, Retinal infarction, Retinal ischaemic, Retinal neovascularisation, retinal vascular disorder, Retinal vascular occlusion, Retinal vascular thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Scleral haemorrhage, and Vitreous haemorrhage.
Seriousness/outcomes	Clinical trials Among the 24 subjects in whom an eye haemorrhage-related adverse event was reported, a serious adverse event was reported in 4 subjects. Post-marketing Among the 442 cases reporting eye haemorrhage-related adverse events in the post-marketing safety database, the events outcomes were reported as follows: 10.9% recovered/resolved, 2.3% recovered/resolved with sequelae, 9.7% recovering/resolving, 28.1% not recovered/not resolved, and 49.1% unknown.

Potential Risk Eye Haemorrhage

Severity and nature of risk

Clinical trials

Among the 24 eye haemorrhage-related adverse events reported, 45.8% (11/24) were considered mild, 37.5% (9/24) were considered moderate, and 16.7% (4/24) were considered severe.

Incidence and Severity of Treatment-Emergent Adverse Events

MedDRA PT	N=24	Severity		
		Mild	Moderate	Severe
Vitreous haemorrhage	3	0	1	2
Conjunctival haemorrhage	6	4	2	0
Scleral haemorrhage	2	1	1	0
Eye haemorrhage	3	2	1	0
Retinal aneurysm	1	0	1	0
Retinal haemorrhage	7	3	3	1
Retinal neovascularisation	1	1	0	0
Retinal vein thrombosis	1	0	0	1

Background incidence/prevalence

There are no published data on occurrence of eye haemorrhage specifically in men with erectile dysfunction. In the Atherosclerosis Risk In Communities (ARIC) study, a US population-based cohort study, estimates of the prevalence of retinopathy (defined as microaneurysms, retinal haemorrhages and soft exudates) ranged over 5 – 12%, depending on presence of metabolic syndrome/syndrome components.[33]

Risk groups or risk factors

None specifically identified.

Potential mechanisms

The effects of sildenafil (ED) on bleeding time and platelet activity have been investigated extensively in preclinical and clinical studies, which demonstrate that the modest anti-platelet activity observed *ex vivo* is not confirmed by a clinically significant effect on bleeding time.

Preventability

There are no known preventive measures.

Impact on individual patient

Eye haemorrhage leads to poor vision. Visual acuity remains moderately impaired in most cases but in few cases may involve total loss of vision.

Potential public health impact of safety concern

A causal relationship has not been established between the use of PDE5 inhibitors and eye haemorrhage. No public health impact is anticipated, based on the current data from the development program and post-marketing data.

Evidence source

Clinical trial and post-marketing data, published literature.

MedDRA terms

MedDRA High-Level Terms (HLTs: (1) HLT Anterior Chamber Bleeding and Vascular Disorders; (2) HLT Choroid and Vitreous Haemorrhages and Vascular Disorders; (3) HLT Conjunctival and Corneal Bleeding and Vascular Disorders; (4) HLT Ocular Bleeding and Vascular Disorders (not elsewhere classifiable); and (5) HLT Retinal Bleeding and Vascular Disorders (Excluding Retinopathy).

7.4. IDENTIFIED AND POTENTIAL INTERACTIONS

7.4.1. Overview of Potential for Interactions

Sildenafil (ED) is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a phophodiesterase (PDE) selectivity profile similar to sildenafil (ED) and an in vitro potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil (ED). The N-desmethyl metabolite is further metabolized, with a terminal half-life of approximately 4 hours. The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

7.4.2. Important Identified and Potential Interactions

7.4.2.1. Identified Drug Interaction

Interacting Substance(s)	**Nitrates**
Effect of interaction	Hypotension is the most serious risk with concomitant nitrates.
Evidence source	Two separate searches of the MAHs safety database were conducted on a total of 39,277 non-clinical study sildenafil (ED) cases received into the database through 15 July 2007 to identify potential drug interactions between sildenafil (ED) and nitrates. The first search was conducted for cases reporting nitrates as co-suspect and/or concomitant medications (478 cases were identified). The second was conducted for cases that reported MedDRA PT of Drug interaction in addition to co-suspect and/or concomitant nitrate medications, as in the first search (93 cases were identified). The five most common nitrates reported as either co-suspect or concomitant medications were glyceryl trinitrate (227 cases), isosorbide dinitrate (128 cases), organic nitrates (88 cases), isosorbide and isosorbide combinations (24 cases), and amyl nitrate (17 cases). The two datasets represent a reporting ratio of 1.2% (478/39,277) and 0.3% (93/39,277), respectively. A total of 37 AEs were reported, which is a comparable reporting rate to that observed with the clinical study data. This analysis showed AEs that were consistent with conditions for which nitrates are prescribed (i.e. cardiovascular conditions) or consistent with the pharmacodynamic interaction between sildenafil (ED) and nitrates, resulting in events relating to hypotension (See SCS Section 2.7.4.5.3.2). An updated search of the MAH's safety database was conducted through 30 June 2013 which identified a total of 625 non-study sildenafil (ED) cases involving concomitant use of a nitrate, out of a total of 62,864 sildenafil (ED) cases. The findings are generally consistent with the previous review.
Possible mechanisms	Consistent with its known effects on the NO/cGMP pathway, sildenafil (ED) was shown to potentiate the hypotensive effects of nitrates.
Potential health risk	Coadministration with nitric oxide donors, such as amyl nitrate or nitrates in any form could result in hypotension.

Interacting Substance(s)	Nitrates
Discussion	Consistent with its known effects on the NO/cGMP pathway and the currently approved sildenafil (ED) label, the concomitant use of sildenafil (ED) is contraindicated with nitric oxide donors or nitrates in any form.

7.4.2.2. Potential Drug Interactions

The potential for drug interactions with sildenafil (ED) has been extensively explored. These data are provided in the Summary of Clinical Pharmacology (Module 2) and in the original written summary. In clinical pharmacology studies for the ED program, cimetidine was found to increase sildenafil (ED) area under the time-concentration curve (AUC) by 56% (study 148-002), erythromycin to increase sildenafil (ED) AUC 2.8 fold (Study 148-234) and saquinavir to increase sildenafil (ED) AUC by 3.1 fold (Study 148-239).

Interacting Substance(s)	CYP3A4 Inhibitors
Effect of interaction	CYP3A4 Inhibitors, such as ritonavir and saquinavir, could increase sildenifil peak concentration (C_{max}) if administered concurrently.
Evidence source	A safety analysis across all studies contained in the original sildenafil (ED) Marketing Authorisation Application (MAA), indicated that the overall frequency of all causality AE was higher for sildenafil (ED) subjects (76%) and placebo subjects (53%) with concomitant CYP3A4 inhibitors than for those for sildenafil (ED) (63%) and placebo (41%) subjects without concomitant CYP3A4 inhibitors. Furthermore, the overall frequency of discontinuation due to adverse events was comparable for sildenafil (ED) (2%) and placebo (3%) subjects with concomitant CYP3A4 inhibitors and sildenafil (ED) (3%) and placebo (3%) subjects without (See SCS Section 2.7.4.5.3.3). It was concluded that sildenafil (ED) was well tolerated in subjects receiving concomitant CYP3A4 inhibitors. Subsequent to sildenafil (ED) approval, further interaction studies with protease inhibitors, the majority of which are CYP3A4 inhibitors, were performed. Ritonavir increased sildenafil (ED) maximum plasma concentrations and exposure to a much greater effect than that observed when sildenafil (ED) was co-administered with steady state saquinavir. However, in both studies, sildenafil (ED) was generally well tolerated, with no serious adverse events and no increased frequency of adverse events or clinically significant changes in laboratory, electrocardiogram (ECG) or vital signs (See SCS Section 2.7.4.5.3.3).
Possible mechanisms	Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Several interaction studies were performed and included in the original MAA submission for the indication of erectile dysfunction to investigate the potential interaction of CYP3A4 inhibitors with sildenafil (ED) (148-002 and 148-234).
Potential health risk	As sildenafil (ED) is administered PRN (maximum of one dose per day), the safety risk of concomitant sildenafil (ED) and CYP3A4 use is likely to be low in the general ED population, even at sildenafil (ED) doses above 25 mg.
Discussion	An integrated review of the clinical and post-marketing data regarding concomitant

Interacting Substance(s)	CYP3A4 Inhibitors
	CYP3A4 inhibitor use identified no new safety issues. The safety profile of sildenafil (ED) in the presence of concomitant CYP3A4 inhibitor use is similar to that of sildenafil (ED) alone with common AEs being consistent with PDE-5 inhibition. Though the current sildenafil (ED) SmPC advises initiation of sildenafil (ED) therapy at 25 mg, whilst taking concomitant CYP3A4 inhibitors, both the clinical and post-marketing data demonstrate that ED patients have taken doses of 50-200 mg sildenafil (ED) without any deleterious adverse effects. Indeed, there appears to be little difference in the safety profile of sildenafil (ED) across doses (25-100 mg) with concomitant CYP3A4 inhibitor use.

Interacting Substance(s)	CYP3A4 Inducers
Effect of interaction	CYP3A4 Inducers, such as rifampin and bosentan, can decrease sildenifil (ED) AUC and C_{max} if administered concurrently
Evidence source	In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max} respectively. Sildenafil increased bosentan AUC and C_{max} by 49.8% and 42%, respectively.
Possible mechanisms	Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inducers of these isoenzymes may increase sildenafil clearance.
Potential health risk	Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil (ED) (CSR A148-1149).
Discussion	A recently completed Pfizer study (A1481243) evaluated the safety and efficacy of concomitant treatment with sildenafil (20 mg TID) and bosentan in the treatment of PAH. Study A1481243 was a randomized, double-blind, placebo controlled study conducted in 103 subjects with PAH who were on bosentan therapy for a minimum of three months. Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy.

Interacting Substance(s)	Alpha-Blockers
Effect of interaction	The concomitant administration of an alpha-blocker and sildenafil (ED) could lead to a decrease in systemic blood pressure that is symptomatic.
Evidence source	Based on 3 formal drug interaction studies of sildenafil (ED) and doxazosin co-administration, a review or 57 sildenafil (ED) placebo-controlled studies, post-marketing data from Pfizer safety database, and the literature the data support that the combination of doxazosin (the most widely used α-blocker) with sildenafil (ED) is generally well tolerated for the vast majority of patients[34]. The concomitant administration of the α-blocker doxazosin (up to 8 mg once daily) and sildenafil (ED) (single doses up to 100 mg) was however observed to lead to a

Interacting Substance(s)	Alpha-Blockers
	decrease in systemic blood pressure that was in some cases symptomatic. An integrated cumulative review of the clinical and post-marketing data regarding concomitant α-blocker use suggests that the frequency of concomitant α-blocker use with sildenafil (ED) was similar in clinical ED studies and post-marketing data (See SCS Section 2.7.4.5.3.1). The safety profile of sildenafil (ED) was comparable in the presence or absence of concomitant use of α-blockers in clinical ED studies. Common adverse events were either known sildenafil (ED) drug reactions from PDE5 inhibition or were associated with potential hypotension consistent with the pharmacodynamic effects expected from a sildenafil (ED)/α-blocker drug interaction.
Possible mechanisms	PDE5 inhibitors, including sildenafil (ED), and alpha-adrenergic blocking agents are both vasodilators with BP lowering effects.
Potential health risk	The concomitant administration of an alpha-blocker and a PDE5 inhibitor, such as sildenafil (ED), can lead to a decrease in systemic blood pressure, causing hypotension in some patients.
Discussion	Though the current sildenafil (ED) SmPC advises that patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil (ED) treatment, and that initiation of sildenafil (ED) should start at lower doses, both the clinical and post-marketing dataset show that patients have taken doses of 50-200 mg sildenafil (ED) and α-blockers without any deleterious effects. There appears to be little difference in the safety profile of sildenafil (ED) across all doses (25-100 mg) with concomitant use of α-blockers. Overall, sildenafil (ED) appears to be well tolerated by subjects receiving concomitant α-blockers. As sildenafil (ED) is to be administered 'prn' (maximum of one dose per day) and is well tolerated in the therapeutic dose range, the safety risk of drug/drug interaction is likely to be reduced, compared to a chronically administered therapeutic. Literature reports support that the combination of doxazosin (the most widely used α-blocker) with sildenafil (ED) is generally well tolerated for the vast majority of patients.[34]

Interacting Substance(s)	Other PDE5 Inhibitors
Effect of interaction	Coadministration of other PDE5 inhibitors with sildenafil (ED) has the potential to cause known PDE5 inhibitor drug reactions.
Evidence source	An integrated review of the clinical and post-marketing data regarding concomitant ED medication use (ie, other PDE5 inhibitors, alprostadil) with sildenafil (ED) treatment suggests the overall frequency of concomitant sildenafil (ED) and other ED medication use is very low. Very few AEs were reported with sildenafil (ED) treatment and concomitant ED medication administration in ED clinical studies. AEs that were reported were either attributed to underlying conditions or were known sildenafil (ED) adverse drug reactions.
Possible mechanisms	Other drugs commonly used to used to treat ED are PDE5 inhibitors and likely would have an additive effect to the sildenafil (ED), possibly exposing patients to additional toxicity

Potential health risk	The potential health risk is minimal if patients adhere to directions in the product label.
Discussion	The current sildenafil (ED) SPC contraindicates the concomitant use of sildenafil (ED) with other treatments for ED.

7.5. PHARMACOLOGICAL CLASS EFFECTS

Sildenafil (ED) was the first PDE5 inhibitor developed and marketed worldwide, including the EU. Since the introduction of sildenafil (ED), several other PDE5 inhibitors have been approved, with tadalafil and vardenafil being the main ones on the market.

7.5.1. Pharmacological Class Risks Already Included as Important Identified or Potential Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Seen with Other Products in Same Pharmacological Class (Source of Data/Journal Reference)
NAION	Rare	Tadalafil- Rare (SmPC) Vardenafil- Not Known (SmPC)
Sudden Hearing loss	Rare	Tadalafil- Rare (SmPC) Vardenafil- Not Known (SmPC)
Eye haemorrhage	Uncommon	Tadalafil- Not reported in SmPC Vardenafil- Not reported in SmPC

Frequency categories defined as: Very Common ≥ 1/10, (≥ 10%), Common ≥ 1/100 and < 1/10, (≥ 1% and < 10%), Uncommon ≥ 1/1000 and < 1/100, (≥ 0.1% and < 1%), Rare ≥ 1/10,000 and < 1/1000, (≥ 0.01% and < 0.1%), Very Rare < 1/10,000, (< 0.01%), Not Known (cannot be estimated from available data)

7.5.2. Important Pharmacological Class Effects Not Discussed Above

None

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PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

Table 1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Nitrate Interaction
Important potential risks	Non-arteritic anterior ischaemic optic neuropathy (NAION) Sudden hearing loss Eye haemorrhage
Missing information	Severe hepatic impairment

PART III: PHARMACOVIGILANCE PLAN

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 June 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

3.1. SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

Below is a summary of planned pharmacovigilance actions for each important identified and potential risk and missing information, presented in Table 1, Table 2 and Table 3, respectively.

Table 1. Safety Concern- Important Identified Risks

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety Concern- Nitrate interaction		
None	Routine pharmacovigilance activities.	To further evaluate the risk of nitrate interaction in patients receiving sildenafil (ED) in normal clinical practice.

Table 2. Safety Concern- Important Potential Risks

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety concern- Non-arteritic anterior ischaemic optic neuropathy (NAION)		
None	Routine Pharmacovigilance	To assess the potential risk of NAION among patients receiving sildenafil (ED).
Safety Concern- Sudden hearing loss		
None	Routine Pharmacovigilance	To further evaluate the risk of deafness/hearing loss in patients receiving sildenafil (ED).
Safety Concern- Eye haemorrhage		
None	Routine Pharmacovigilance	To closely monitor and further evaluate the risk of eye haemorrhage in patients receiving sildenafil (ED).

Table 3. Missing Information

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety concern- Severe hepatic impairment		
None	Routine Pharmacovigilance	To monitor for adverse events and further evaluate for the possibility of a risk in this population

3.2. Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

There are no additional ongoing or planned pharmacovigilance activities to assess the effectiveness of risk minimization measures.

3.3. Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Study/Activity Title; Study A1481282- Non-Interventional Study to Characterise the Epidemiology of NAION	
Safety concern(s)/risk minimisation measure investigated	Descriptive non-interventional study to characterise the epidemiology of non-arteritic anterior ischaemic optic neuropathy (NAION)
Brief summary of results	This large descriptive study characterised the epidemiology of NAION, including its incidence and associations with potential risk factors. Using medical record review and an algorithm developed to identify NAION cases from a large insurance claims database of more than 16 million members, 1,283 cases were retrospectively identified during 2003-2007. The overall incidence of NAION was estimated at 0.05 cases per 1,000 person-years; among men 45+ years, the incidence was estimated at 0.10 cases per 1,000 person-years. PDE5 inhibitor use was not associated with increased risk of NAION; among males, the odds ratio for the association between recent PDE5 inhibitor use and NAION was 0.52 (95% confidence interval: 0.28, 0.98). Variables associated with NAION included male sex, diabetes, use of anti-platelet agents, and other markers for underlying cardiovascular disease.
Implications	These findings should be interpreted in light of the limitations of using the claims-based algorithm to identify NAION cases. This algorithm was developed for two reasons: (1) NAION is extremely rare, and claims data provided an opportunity to identify a relatively large sample of cases; and (2) there is no diagnosis code for NAION specifically, necessitating a way of distinguishing NAION cases from non-cases among patients with a claim associated with a diagnosis code for ischemic optic neuropathy. However, the claims-based algorithm demonstrated a low positive predictive value in making this distinction. The low predictive value is likely due to the fact that NAION diagnosis is not the product of a standard set of diagnostic criteria applied to tests that can be readily identified through claims, but rather is based on a composite of history, symptoms, and diagnostic findings. This mix of clinical inputs to the diagnosis of NAION may not lend itself to algorithmic identification through claims associated with diagnoses, procedures, and drug dispensing codes. Nonetheless, the incidence estimates from this study are consistent with the literature. Further, a similar odds ratio for the association between PDE5 inhibitor use and NAION was observed when the analysis was limited to cases identified by expert adjudication of medical records (ie, cases highly likely to represent true NAION); removing the cases identified by the claims-based algorithm did not materially affect the estimate.

Study/Activity Title; Study A1481259- Case-crossover Study of PDE5 Inhibitor Exposure as a "Trigger Factor" for Acute NAION	
Safety concern(s)/risk minimisation measure investigated	Examine whether use of PDE5 inhibitors, triggers the onset of acute NAION
Brief summary of results	An observational, non-interventional, case-crossover study (A1481259) was conducted to examine whether as-needed use of PDE5i, as a class (including sildenafil, vardenafil, or tadalafil) triggers the onset of acute NAION within a pharmacokinetically-defined time period (approximately 5 half-lives) following drug ingestion. In the primary analysis, the PDE5i exposure status of the day preceding NAION symptom onset (the case window) was compared with the PDE5i exposure status of the 29 days preceding the case window (the 29 control windows). A total of 673 subjects who met the potential acute NAION case criteria were enrolled from 102 sites during October 2008 to October 2012 (66 sites in the US, 3 in the United Kingdom, 8 in France, 10 in Germany, 7 in Italy, and 8 in Spain). Seventy-six (76) subjects were exposed and 597 subjects were unexposed to PDE5i in the 60 days prior to NAION symptom onset. For the 76 exposed subjects, the mean age was 61.6 years (range: 45 to 81 years); most subjects were white (86.8%). For the 597 subjects with no exposure, the mean age was 62.3 years (range: 45 to 88 years); most subjects were white (85.6%). For the 43 Definite NAION cases, the estimated odds ratio (OR) was 2.15 and the 95% confidence interval (CI) was (1.06, 4.34) based on classical linear regression (CLR); this OR suggests a 2.15-fold increase in the odds of acute NAION onset within 5 half-lives of PDE5i use as compared with PDE5i use prior to the pharmacokinetically-defined time window but within the 30 days prior to onset. In the sensitivity analysis including the 64 "definite" and "possible" cases combined, the OR was 2.36 and the 95% CI was (1.33, 4.19) based on CLR. This OR suggests a 2.36-fold increase in the odds of acute NAION onset within 5 half-lives of PDE5 inhibitor use as compared with PDE5 inhibitor use prior to the pharmacokinetically-defined time window but within the 30 days prior to onset. Adverse events: 8 SAEs were retrospectively reported for 2 subjects; none of these events was attributed to sildenafil (ED). Eight (8) non-serious AEs for 6 subjects were reported by the investigator; one of these events, headache, was attributed to sildenafil (ED). No deaths were reported. The primary analysis of Definite NAION cases suggests an approximately 2-fold increased risk of NAION within 5 half-lives of PDE5 inhibitor use; given that the outcome is rare, the OR may be interpreted as an estimate of the relative risk. Varying the definition of the outcome (ie, including Possible NAION cases) or the imputation rule for dates of uncertain instances of use does not materially affect this finding. Although bias from inaccuracies in recall of exposure and exposure-based enrollment cannot be excluded, evidence suggests that these sources of bias were unlikely to have substantially affected the results.

Study/Activity Title; Study A1481259- Case-crossover Study of PDE5 Inhibitor Exposure as a "Trigger Factor" for Acute NAION	
Implications	To put these findings into context, the absolute risk (ie, risk difference) was estimated by applying the estimated OR of 2.36 based on subjects adjudicated as "definite" or "possible" NAION cases to an estimate of the background annual risk of NAION and accounting for the average proportion of days in a given year that a PDE5i user is exposed. Using conservative assumptions, PDE5i use is estimated to add 3 to 8 cases per 100,000 males 50 years and older per year.

3.4. Details of Outstanding Additional Pharmacovigilance Activities

There are no outstanding additional pharmacovigilance activites.

3.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

There are no imposed mandatory additional pharmacovigilance activities.

3.4.2. Mandatory Additional PhV Activity (Being a Specific Obligation)

There are no mandatory additional pharmacovigilance activities.

3.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Not applicable

3.4.4. Stated Additional Pharmacovigilance Activities

Not applicable

3.5. SUMMARY OF THE PHARMACOVIGILANCE PLAN

The pharmacovigilance plan for sildenafil (ED) at present is comprised of routine pharmacovigilance activities. There are no ongoing or planned additional studies or activities. Completed studies/activities are summarized in Table 4.

Table 4. Table of Completed Studies/Activities from the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Completed)	Date of Submission of Final Study Report
Epidemiologic study A1481282: The Detection and Epidemiology of NAION in a Commercially Insured Population in the United States	Description of incidence, natural history and potential risk factors of NAION	Epidemiology of non-arteritic anterior ischaemic optic neuropathy (NAION) was characterised; in addition, the association between PDE5 inhibitor use and NAION was estimated	Completed	March 2010
Epidemiologic study: A1481259: Case-crossover Study of PDE5 Inhibitor Exposure as a "Trigger Factor" for Acute NAION	To examine whether as-needed use of PDE5i, as a class (including sildenafil, vardenafil, or tadalafil) triggers the onset of acute NAION within a pharmacokinetically-defined time period (approximately 5 half-lives) following drug ingestion.	Examined whether use of PDE5 inhibitors triggers the onset of acute NAION	Completed	April 2013
Prescription Event Monitoring Study (Phase I and II); Cohort study[1,2]	A population-based study conducted in 2 phases to measure the occurrence of safety outcomes, including selected short-term cardiovascular events, in patients prescribed sildenafil (ED) in England	Estimated the rates of various adverse events, including fatal myocardial infarction and ischaemic heart disease (IHD), among patients prescribed sildenafil in England; rates of fatal myocardial infarction/IHD and fatal IHD separately were compared with the rate in the general population	Completed	Nov 2002

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Completed)	Date of Submission of Final Study Report
International Men's Health Study; Cohort study[3]	A prospective cohort study designed to assess the incidence of serious cardiovascular disease (CVD) events [ie, myocardial infarction (MI) and stroke] and all-cause mortality in men with erectile dysfunction (ED) who received prescriptions for sildenafil (ED) in Germany, France, Spain, and Sweden	Estimated the incidence of all-cause mortality, MI and stroke among men with ED who received sildenafil prescriptions in Germany, France, Spain, and Sweden overall, and within subgroups defined by baseline severity of ED and presence of multiple risk factors for CVD	Completed	March 2005

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PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

4.1. APPLICABILITY OF EFFICACY TO ALL PATIENTS IN THE TARGET POPULATION

The ED patient population who were enrolled in the pivotal Phase 3 studies of sildenafil (ED) was intended to be reflective of the population who would be expected to be prescribed sildenafil (ED) in clinical practice. This clinical program was designed to exclude subjects in the following sub-groups: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa.

The clinical trials were designed to enroll subjects as close as possible to the target population; however, the inclusion and exclusion criteria influence the overall applicability of the data generated in these studies. In the clinical practice setting, there will be subjects who are on concurrent medications or co-morbidities that may affect the medical outcome.

4.2. TABLES OF POST-AUTHORISATION EFFICACY STUDIES

There are no ongoing post-authorisation efficacy studies for sildenafil (ED), and none are planned.

PART V: RISK MINIMISATION MEASURES

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

Data lock point for current RMP	30 Jun 2013	Version number	3.2
Date of final sign off	26 Nov 2013		

5.1. RISK MINIMISATION MEASURES BY SAFETY CONCERN

Safety Concern	**Nitrate interaction**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of nitrate interaction, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.3: 'Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.' SmPC Section 4.4: 'Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.' SmPC Section 4.5: 'Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.'
Additional risk minimisation measure(s)	None proposed
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimize risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of concomitant nitrate use.
Comment	None.

Safety Concern	**NAION**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of this event, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.3: Sildenafil (ED) is contraindicated in 'Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure' SmPC Section 4.4: The following text is included in Section 4.4 'Special warnings and precautions for use' of the SmPC. 'Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking VIAGRA and consult a physician immediately.' SmPC Section 4.8: NAION is listed as an adverse reaction.
Additional risk minimisation measure(s)	None proposed
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimize risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of NAION.
Comment	None.

Safety Concern	**Sudden Hearing Loss**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of this event, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.8: Deafness is listed as an adverse reaction.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimize risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of occurrence of sudden hearing loss.
Comment	None.

Safety Concern	Eye Haemorrhage
Objective(s) of the risk minimisation measures	Not applicable.
Routine risk minimisation measures	None proposed.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	None.

5.2. RISK MINIMISATION MEASURE FAILURE (IF APPLICABLE)

Not applicable

5.2.1. Analysis of Risk Minimisation Measure(s) Failure

Not applicable

5.2.2. Revised Proposal for Risk Minimisation

Not applicable

5.3. SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified Risks		
Nitrate interaction	The prescriber is informed about the risk of interaction with nitrates through text in the Summary of Product Characteristics (SmPC), and the patient through the Patient Information Leaflet (PIL). SmPC sections: 4.3 Contraindications 4.4 Special warning and precautions for use 4.8 Undesirable effects PIL sections: 2. What you need to know before you take VIAGRA 4. Possible side effects	None proposed
Important potential risks		
NAION	The prescriber is informed about the risk of NAION through text in the SmPC, and the patient through the PIL. SmPC sections: 4.3 Contraindications 4.4 Special warning and precautions for use 4.8 Undesirable effects PIL sections: 2. What you need to know before you take VIAGRA 4. Possible side effects	None proposed
Sudden Hearing loss	The prescriber is informed about the risk of sudden hearing loss through text in the SmPC, and the patient through the PIL. SmPC sections: 4.8 Undesirable effects PIL sections: 4. Possible side effects	None proposed
Eye haemorrhage	None proposed	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information		
Severe hepatic impairment	The prescriber is informed about use in patients with severe hepatic impairment through text in the SmPC, and the patient through the PIL. <u>SmPC sections:</u> 4.2 Posology and method of administration 4.3 Contraindications <u>PIL sections:</u> 2. What you need to know before you take VIAGRA	None proposed

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

Active substance(s) (INN or common name):	Sildenafil citrate
Pharmaco-therapeutic group (ATC Code):	G04B E03
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	VIAGRA SILDENAFIL PFIZER VERVENTI

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6.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

6.1.1. Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Nitrate Interaction
Important potential risks	Non-arteritic anterior ischaemic optic neuropathy (NAION) Sudden hearing loss Eye haemorrhage
Missing information	Severe hepatic impairment
New identified safety concern	None

6.1.2. On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

There are no ongoing or planned additional studies in the pharmacovigilance plan.

6.1.3. Summary of Post Authorisation Efficacy Development Plan

There are no planned post-authorisation efficacy studies.

6.1.4. Summary Table of Risk Minimisation Measures

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Nitrate interaction	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.3: 'Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.' SmPC Section 4.4: 'Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.' SmPC Section 4.5: 'Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide	None

	donors or nitrates in any form is therefore contraindicated.' Risks will be further characterised through routine pharmacovigilance activities to determine if further risk minimisation activities are required.	
Non-arteritic anterior ischaemic optic neuropathy (NAION)	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.3: Sildenafil (ED) is contraindicated in 'Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure' SmPC Section 4.4: The following text is included in Section 4.4 'Special warnings and precautions for use' of the SmPC. 'Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking VIAGRA and consult a physician immediately.' SmPC Section 4.8: NAION is listed as an adverse reaction. Risks will be further characterised through routine pharmacovigilance activities to determine if further risk minimisation activities are required.	None

Sudden hearing loss	Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.8: Deafness is listed as an adverse reaction. Risks will be further characterised through routine pharmacovigilance activities to determine if further risk minimisation activities are required.	None
Eye haemorrhage	None proposed	None
Severe hepatic impairment	The prescriber is informed about use in patients with severe hepatic impairment through text in the SmPC, and the patient through the PIL. SmPC sections: 4.2 Posology and method of administration 4.3 Contraindications PIL sections: 2. What you need to know before you take VIAGRA	None proposed

6.2. ELEMENTS FOR A PUBLIC SUMMARY

6.2.1. Overview of Disease Epidemiology

Erectile dysfunction (ED) is the inability of a man to develop or maintain an erection during sexual activity. An erection of the penis is the result of blood entering and temporarily remaining in the penis during sexual arousal and requires proper functioning of the brain, hormones, heart, blood vessels, and nerves. As a result, ED can be caused by psychological factors, as well as heart, blood vessel, nervous, and hormonal factors. Erectile dysfunction increases in frequency with increasing age. For example, about 25% of men in their 50s have ED compared with 45% of men in their 60s.[1,2,3,4] Erectile dysfunction may occur more commonly in men who have heart or blood vessel disease, diabetes, obesity, high blood pressure, nerve damage due to injury or surgery for prostate cancer, or who smoke or drink excessively.[5],[6,7,8]

6.2.2. Summary of Treatment Benefits

Clinical studies show that at a range of doses from 5 mg to 200 mg, sildenafil (ED) was effective in improving the ability to achieve and maintain erections sufficient for sexual intercourse and was most effective in the range of 25 mg to 200 mg.

Sildenafil (ED) is effective in treating erectile dysfunction from all common causes, including diabetes and spinal cord injury. Diabetic patients and patients who have had their prostate removed did not obtain as good a response to sildenafil (ED) as patients who did not have these conditions.

6.2.3. Unknowns Relating to Treatment Benefits

In the clinical program the majority of patients were white. There is no reason to believe that members of other racial groups are affected differently. The following sub-groups of patients were not studied in sildenafil (ED) clinical trials: patients with severe liver disease, low blood pressure, recent history of stroke or heart attack, and certain inherited conditions of the eye. Another form of sildenafil is used for the treatment of high blood pressure in the lungs. However, sildenafil (ED) has not been studied for this use.

6.2.4. Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Interaction with drugs containing nitrates (nitrate interaction).	A patient who is taking a drug that contains nitrates, such as glyceryl trinitrate and isosorbide dinitrate, could have a serious drop in blood pressure after taking sildenafil (ED).	The doctor who prescribes sildenafil (ED) will be warned by the product label about the risk of low blood pressure in patients who take drugs containing nitrates.

Important Potential Risks

Risk	What is Known	Preventability
Interruption of the blood supply to the main nerve of the eye (non-arteritic anterior ischaemic optic neuropathy [NAION]).	There is a risk that patients taking sildenafil (ED) could develop visual changes caused by interruption in blood flow within the eye.	The doctor who prescribes sildenafil (ED) will be warned by the product label about the risk of interruption of blood flow to the eye.
Bleeding within the eye (eye haemorrhage)	There is a risk that patients taking sildenafil (ED) could develop visual changes caused by bleeding within the eye.	The doctor who prescribes sildenafil (ED) will be warned by the product label about the risk of eye bleeding.
Sudden hearing loss	There is a risk that patients taking sildenafil (ED) could develop a sudden hearing loss	The doctor who prescribes sildenafil (ED) will be warned by the product label about the risk of sudden hearing loss.

Missing Information

Risk	What is Known
Serious liver disease or injury	Because sildenafil (ED) was not studied in patients who have serious liver

(severe hepatic impairment)	disease or injury, little is known about how people with liver problems are affected by sildenafil (ED).

6.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for sildenafil (ED) can be found in sildenafil (ED)'s EPAR page.

This medicine has no additional risk minimisation measures.

6.2.6. Planned Post Authorisation Development Plan

No post-authorisation development plan is proposed.

Studies which are a Condition of the Marketing Authorisation

No studies were required as a condition of marketing authorisation.

6.2.7. Summary of Changes to the Risk Management Plan over Time

Table 1. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comment
1.4 Revatio/Viagra RMP	February, 2006	First addition of sildenafil (ED) (Viagra) to the sildenafil (PAH) (Revatio) RMP Identified Risk: None Potential Risk: NAION Missing Information: None 1) Response to Rapporteur, Final Assessment Report, EMEA/H/C/638/SOB/002 2) Viagra –FUM 16 – Follow up measures. EMEA/424217/2005.	None
3.0 Viagra RMP	April 2009	Request from EMEA to split the Revatio/Viagra RMP v. 2.1 into 2 individual RMPs. Inclusion of nitrate interaction as an important identified risk for Viagra. Inclusion of detailed PhV Plan for new safety concern (sudden hearing loss)	None

		Update on NAION FUM. Inclusion of CYP3A4 inhibitors, alpha blockers, and other MED medications as potential drug interactions.	
3.1 Viagra RMP	July 2009	Conclusions of the EMEA Rapporteur's Assessment Report of Viagra RMP version 3.0, as adopted by the CHMP on 23 July 2009. Detailed description of potential risk of sudden hearing loss inserted.	None

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[4] Shaeer, K., et al., Prevalence of erectile dysfunction and its correlates among men attending primary care clinics in three countries: Pakistan, Egypt, and Nigeria. *International Journal of Impotence Research* 2003. 15(Suppl 1): p. S8-S14.

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[8] Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol* 1994; 140: 1003 8.

ANNEX 7. SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

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Not applicable

ANNEX 10. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

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Not applicable