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

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

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. <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

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

References

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[3] Nicolosi A., et al., Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. *International Journal of Impotence Research* 2003; 15: 253-7.

[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.

[5] Shaeer O, Shaeer K. The Global Online Sexual Survey (GOSS): The United States of America in 2011. Chapter 1: Erectile dysfunction among English-Speakers. *J Sex Med* 2012;9:3018-27.

[6] Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; 51: 54-61.

[7] Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol* 1994; 140: 930-7.

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