4 Part VI: Summary of activities in the risk management plan by product

4.1 Part VI.1 Elements for summary tables in the EPAR

Table 4-1 Part VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	Increased relative mortality in pediatric population
	Vaso-occlusive crisis in patients with sickle cell anaemia
	Epistaxis/Bleeding events
	Interaction with organic nitrates
	Interaction with bosentan (and other CYP3A4 Inducers)
Important identified risks	Non-arteritic anterior ischemic optic neuropathy (NAION)
	Hypotension
	Pulmonary hemorrhage in pediatric population
	Hearing loss
	Drug interaction with epoprostenol, iloprost, alpha blockers, other PDE5 inhibitors
Missing information	Use in pregnancy
	Safety in patients with cardiovascular disease
	Long term mortality
	Long term ocular safety
	Safety in patients with renal impairment

Table 4-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None

Table 4-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None

Table 4-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Increased relative mortality in pediatric population	Guidance is provided in section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties of the SmPC.	None
Vaso-occlusive crisis in patients with sickle cell anemia	Guidance is provided in section 4.4 Special warnings and precautions for use of the SmPC.	None
Epistaxis/Bleeding events	Guidance is provided in section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects of the SmPC.	None
Interaction with organic nitrates	Guidance is provided in section 4.3 Contraindications, and section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.	None
Interaction with bosentan (and other CYP3A4 inducers)	Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.	None
Non-arteritic anterior ischemic optic neuropathy (NAION)	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Hypotension	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.1 Pharmacodynamic properties of the SmPC.	None
Pulmonary hemorrhage in pediatric population	Currently available data do not support the need for risk minimization.	None
Hearing loss	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Drug interaction with epoprostenol, iloprost, alpha blockers and other PDE5 inhibitors	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects of	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	the SmPC.	
Use in pregnancy	Guidance is provided in section 4.6 Fertility, pregnancy and lactation of SmPC.	None
Safety in patients with cardiovascular disease	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.8 Undesirable effects and section 5.1 Pharmacodynamic properties of SmPC.	None
Long term mortality	Guidance is provided in section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties of SmPC.	None
Long term ocular safety	Guidance is provided in section 4.4 Special warnings and precautions for use and section4.8 Undesirable effects of the SmPC.	None
Safety in patients with renal impairment	Guidance is provided in section 4.2 Posology and method of administration and section 5.2 Pharmacokinetic properties of the SmPC.	None

4.2 Part VI.2 Elements for a Public Summary

4.2.1 Part VI.2.1 Overview of Disease Epidemiology

Pulmonary Arterial Hypertension (PAH) in Adult:

Pulmonary hypertension (increase of blood pressure in the lung blood vessels) is a chronic (long term) disorder of heart and lung leading to right heart failure (heart is unable to pump enough blood to meet the body's needs), and is an important cause of death and disability all over the world. [Eliot CG, 2010]. The number of cases of PAH in the US has been estimated as 109 per million among individuals under 65 years of age, and 451 per million among individuals 65 years of age and over. It has been found that PAH is more likely to be diagnosed in women than men and the survival among PAH patients has been reported to be 83% at 1 year and 58% at 3 years [Sikirica M, 2014]. Each year in Europe and North America 1-3 cases of idiopathic (cause of disease is unknown) PAH and 2-5 cases of associated PAH are diagnosed per million inhabitants [Eliot CG, 2010].

Pulmonary Arterial Hypertension in Paediatric:

PAH is a rare disease both for children and adults [Widlitz A, 2003]. The type of PAH most common in children is idiopathic PAH and PAH associated with congenital heart disease (birth heart defects) [Vorhies EE, 2014]. According to data from Netherlands the yearly occurrence for pulmonary hypertension was 63.7 cases per million children [Ivy DD, 2013]. Without appropriate treatments, survival in children after diagnosis with idiopathic PAH might be worse compared to adults, and was 10 months for children according to data from National Institutes of Health, US. Reports from the United Kingdom and Netherlands have shown variable but improved survival rates in children with PAH [Vorhies EE, 2014]. The gender of children patients with primary pulmonary hypertension is 1.8:1 females:males, with no significant difference in the younger children compared with the older children [Widlitz A, 2003].

4.2.2 Part VI.2.2 Summary of treatment benefits

Single dose of oral sildenafil is a more effective and selective pulmonary vasodilator (helps in expanding the blood vessels of lung only but not the rest of the body) compared with the gold standard (standard treatment), inhaled nitric oxide (iNO), in decreasing the mean pulmonary artery pressure (pressure in the lung blood vessel) and equally effective and selective in reducing pulmonary vascular resistance (force opposing the flow across the lung blood vessels). The preferential effect of sildenafil on the pulmonary circulation suggests that sildenafil might be superior to iNO in the evaluation of the patients with severe pulmonary hypertension and might have important safety implications both for the acute study and for eventual long-term use of this drug in patients with left ventricular dysfunction [Michelakis E, 2002].

Sildenafil improves sexual function in men with erectile dysfunction (inability to develop or maintain an erection of the penis during sexual activity). The therapeutic response to sildenafil was similar in men with various causes of erectile dysfunction [Goldstein I, 1998]. Sildenafil is the most common used to treat erectile dysfunction in outpatients in China and elsewhere. According to a large survey of total 1922 valid questionnaires, after 4 weeks of treatment, sildenafil significantly facilitated the sexual activity, self-confidence, mental status, and improved the quality of sexual life [Tang WH, 2015].

4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are no data for the use of sildenafil in pregnant women. There are no data regarding the risk of pulmonary haemorrhage in the pediatric population.

4.2.4 Part VI.2.4 Summary of safety concerns

Table 4-5 Important identified risks

Risk	What is known	Preventability
Increased relative mortality in pediatric population (increased number of deaths in children)	In some long term studies on children an increase in deaths was observed in patients taking doses higher than the recommended dose.	Tablet and suspension powder of sildenafil should not be given to children below 1 year of age and injection should not be given to children below 18 years. Doses higher than the recommended doses should not be used in children suffering with PAH. Medicine should be kept out of the sight and reach of children.
Vaso-occlusive crisis in patients with sickle cell anemia (painful complication of in adolescents and adults where the circulation of blood vessels is obstructed by abnormally (sickle) shaped red blood cells)	It is shown in a study that sildenafil leads to vaso-occlusive crisis requiring hospitalization in patients with sickle cell anaemia	Talk to doctor before taking sildenafil if patient has sickle cell anaemia.
Epistaxis/Bleeding events (Bleeding from nose and other bleeding events)	One of the common side effects of sildenafil are bleeding at the back of the eye and nosebleed and bleeding from penis is one uncommon side effect of sildenafil in adults. One of the very common side effects of sildenafil in children and adolescents is nosebleed.	Patient should talk to doctor before taking sildenafil if they have bleeding disorder (such as hemophilia) or problems with nose bleeds.
Interaction with organic nitrates	Nitrates have blood pressure lowering effects and when taken with sildenafil this effect can be increased.	Patient should not take sildenafil if they are taking medicines containing nitrates, or nitric oxide donors such as amyl nitrate (“poppers”). These medicines are often given for relief of chest pain (or “angina pectoris”). Sildenafil can cause a serious increase in the effects of these medicines. Patient should tell doctor if they are taking any of these medicines, and should ask doctor or pharmacist if not certain.

Risk	What is known	Preventability
Interaction with bosentan (different medication for pulmonary hypertension) (and other CYP3A4 inducers (such as HIV antivirals, glucocorticoids, several antiepileptic medications)	Co-administration of bosentan and sildenafil can lead to a significant decrease of sildenafil blood levels. Patients using drugs such as carbamazepine, phenytoin, phenobarbital, St. John´s wort and rifampicin should be monitored closely for efficacy of sildenafil.	Patients co-administering these drugs with sildenafil need to be closely monitored for efficacy of sildenafil.

Table 4-6 Important potential risks

Risk	What is known
Non-arteritic anterior ischemic optic neuropathy (NAION) (loss of vision because of a problem with blood flow to the nerve in the eye)	Patient should not take sildenafil if they have ever had loss of vision because of a problem with blood flow to the nerve in the eye called non-arteritic anterior ischemic optic neuropathy (NAION).
Hypotension (low blood pressure)	Patient should not take sildenafil if they have very low blood pressure (<90/50 mmHg). Patient should talk to doctor before taking sildenafil if they have low blood pressure at rest. One of the common side effects of sildenafil is low blood pressure in adults.
Bleeding of the lung in children (Pulmonary hemorrhage in pediatric population)	There is no sufficient data available for the assessment of an association of sildenafil with pulmonary hemorrhage in the pediatric population.
Hearing loss	Sudden decrease or loss of hearing has been reported as a side effect of sildenafil but occurrence rate is unknown. Hearing impairment has been reported as an uncommon serious adverse effect of sildenafil in children and adolescents.
Drug interaction with epoprostenol, iloprost, alpha blockers and other PDE5 inhibitors (such as tadalafil, vardenafil, theophylline, theobromine (for erectile dysfunction or pulmonary hypertension))	Co-administration with these drugs may lead to low blood pressure.

Table 4-7 Missing information

Risk	What is known
Use in pregnancy	Patient should ask doctor or pharmacist for advice before taking this medicine if pregnant, or breast-feeding, if may be pregnant or are planning to have a baby. Sildenafil should not be used during pregnancy unless strictly necessary. Sildenafil should not be given to women of child bearing potential unless using appropriate contraceptive methods (methods or devices used to prevent pregnancy).

Risk	What is known
Safety in patients with cardiovascular disease	Patient should not take sildenafil if they have recently had a stroke or a heart attack. Patient should talk to doctor before taking sildenafil if they have a severe heart problem or a problem with the pumping chambers of heart.
Long term mortality	In the long term studies in children, an increase in deaths was observed in patients given doses higher than the recommended dose. Therefore, doses higher than the recommended doses should not be used in children with pulmonary arterial hypertension.
Long term ocular safety	Patient should talk to doctor before taking sildenafil if they have retinitis pigmentosa (rare inherited eye disease). When used to treat male erection disorder or impotence (inability to develop or maintain an erection of the penis during sexual activity), the following visual side effects have been reported with PDE5 inhibitors, including sildenafil at an unknown frequency; partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes. Patient should contact physician immediately if experiences any sudden decrease or loss of vision, bleeding at the back of the eye, light sensitivity, effects on color vision.
Safety in patients with kidney (renal) impairment	In patients with mild to moderate renal impairment the clearance of sildenafil was not altered. However, in patients with severe renal impairment, clearance of sildenafil is reduced resulting in an increased concentration of sildenafil and its metabolites.

4.2.5 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has no additional risk minimization measures.

4.2.6 Part VI.2.6 Planned post authorization development plan

None

4.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable (first submission)