VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pulmonary arterial hypertension (PAH) is a disease which causes increased blood pressure in the lungs and can lead to right heart failure and early death. Hypertension occurs when most of the very small arteries throughout the lungs narrow in diameter, which increases the resistance to blood flow through the lungs. Shortness of breath during exertion and fainting spells are the most common symptoms of PAH. People may also experience additional symptoms such as dizziness, swelling of the ankles or legs, chest pain, and a racing pulse. PAH is a rare disease, with an estimated prevalence ranging from 10 to 52 cases per million. PAH can have an unknown cause (idiopathic), a genetic cause (heritable), or be associated with other causes such as HIV-infection. It occurs more often in women and elderly patients. The mean age at diagnosis is around 45 years, although the onset of symptoms can occur at any age.

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, sildenafil represents an effective drug in the treatment of adults, children and adolescents (from 1 to 17 years old) with high blood pressure in the blood vessels in the lungs (pulmonary arterial hypertension).

The product brings down blood pressure in the lungs by widening the blood vessels in the lungs.

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, sildenafil can be considered effective in the approved indications.

VI.2.3 Unknowns relating to treatment benefits

There are no adequate data from the use of sildenafil (PAH) in pregnant women, and in children below 1 year of age. <Sildenafil> 20 mg Film-coated tablets has not been studied in the following sub-groups of patients: patients with severe hepatic impairment, patients with recent history of stroke or myocardial infarction, and patients with severe hypotension (blood pressure < 90/50 mmHg) at initiation.

VI.2.4 Summary of safety concerns

IMPORTANT IDENTIFIED RISKS

Risk	What is known	Preventability
Interaction with drugs containing nitrates, bosentan (and other CYP3A4 inducers[#]) [#] *Drugs which may increase sildenafil clearance*	Sildenafil (PAH) may potentiate the hypotensive effects of nitrates, and therefore it should not be used concurrently with nitric oxide donors (such as amyl nitrite) or nitrates in any form. Sildenafil metabolism is principally mediated by CYP3A4 (major route) and CYP2C9 (minor route). Therefore, inducers of these isoenzymes may increase sildenafil clearance. Dose adjustments for sildenafil may be required when co-administered with CYP3A4 inducers. The efficacy of sildenafil in patients already on bosentan (a moderate inducer of CYP3A4) therapy has not been conclusively demonstrated. Co-administration of bosentan with sildenafil showed a decrease in sildenafil exposure with bosentan co-administration, and increase of bosentan with sildenafil co-administration.	The patients should inform their doctor or pharmacist if they are taking, have recently taken or might take medicines containing nitrates, or nitric oxide donors such as amyl nitrate ("poppers"). The patients should not take sildenafil if they are taking these drugs. The patients should inform their doctor or pharmacist if they are taking, have recently taken or might take - therapies for pulmonary hypertension such as bosentan, and /or - medicines containing St. John's Wort (herbal medicinal product), rifampicin (used to treat bacterial infections), carbamazepine, phenytoin and phenobarbital (used, among others, to treat epilepsy).
Vaso-occlusive crisis in patients with sickle cell disease	The vaso-occlusive crisis, or sickle cell crisis, is a common painful complication of sickle cell disease in adolescents and adults. Acute episodes of severe pain (crises) are the primary reason that these patients seek medical care in hospital emergency departments. Acute pain in patients with sickle cell disease is caused by ischemic tissue injury resulting from the occlusion of microvascular beds by sickled erythrocytes during an acute crisis. Chronic pain occurs because of the destruction of bones, joints and visceral organs as a result of recurrent crises. Sildenafil (PAH) should not be used in patients with pulmonary hypertension secondary to sickle cell anaemia.	The patients should inform their doctor or pharmacist if they have an abnormality of red blood cells (sickle cell anaemia).
Increased relative mortality in the paediatric population	In a paediatric study, an increased number of deaths was observed in paediatric patients administered doses higher than the recommended dose of sildenafil (PAH).	Higher doses should not be used in children. The product should not be given to children below 1 year of age.

Risk	What is known	Preventability
Epistaxis (nosebleed)/ bleeding events	Sildenafil (PAH) may cause nosebleed or other bleeding events. In adults nosebleed may occur commonly (may affect up to 1 in 10 people), and in children and adolescents this event is a very common side effect (may affect more than 1 in 10 people). In adults bleeding at the back of the eye may occur commonly, and penile bleeding uncommonly (may affect 1 in 100 people).	If the patients get nosebleed or other bleeding event, they should inform their doctor or pharmacist. The patients should inform their doctor or pharmacist if they have a bleeding disorder (such as haemophilia) or problems with nose bleeds.

IMPORTANT POTENTIAL RISKS

Risk	What is known (including reason why it is considered a potential risk)
Hypotension	Sildenafil (PAH) may cause decrease in blood pressure. The patients must not take the drug if they have very low blood pressure (<90/50 mmHg).
Non-arteritic anterior ischaemic optic neuropathy (NAION; interruption of the blood supply to the main nerve of the eye)	There is a risk that patients taking sildenafil (PAH) could develop visual changes caused by the interruption in blood flow within the eye. Cases of NAION, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other phosphodiesterase-5 inhibitors. Sildenafil (PAH) should not be used in patients who have loss of vision in one eye because of NAION, regardless of whether this episode was in connection or not with previous phosphodiesterase-5 inhibitor exposure.
Hearing loss	There is a risk that patients taking sildenafil (PAH) could experience hearing loss.
Pulmonary haemorrhage (bleeding) in off-label paediatric patients	There is at present insufficient evidence to establish a causal relationship between pulmonary haemorrhage and sildenafil in off-label paediatric population. The severe underlying disease, co-morbidities and co-medications of this vulnerable group of children may provide an alternative explanation for the events of pulmonary haemorrhage. The product should not be given to children below 1 year of age.
Drug interactions with epoprostenol, iloprost, other PDE5 inhibitors and alpha blockers	Data from use of sildenafil in PAH patients co-prescribed epoprostenol demonstrated a favourable risk/benefit compared with epoprostenol alone. Currently there are no controlled data for the use of sildenafil in iloprost treated PAH patients. Sildenafil belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products has not been studied in PAH patients and such concomitant use is not recommended. Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the combination of the two medicines may cause symptoms resulting in the lowering of your blood pressure (e.g. dizziness, light headedness).

MISSING INFORMATION

Risk	What is known
Long-term ocular safety	Chronic sildenafil treatment up to 80 mg three times a day for PAH did not affect ability to distinguish detail (visual acuity), pressure in the eye (intraocular pressure), or ability to perceive contrast (contrast sensitivity) during treatment in clinical studies. There was no evidence of eye toxicity associated with chronic sildenafil.
Safety in pregnancy	Because sildenafil (PAH) was not studied in pregnant women, little is known about how sildenafil affects pregnant women or their newborns. No evidence of harm was identified in animal studies.
Safety in patients with renal impairment	Because sildenafil (PAH) was not studied in patients with kidney impairment, little is known about how people with kidney problems are affected by sildenafil (PAH).
Safety in patients with cardiovascular diseases	There was no excess cardiovascular serious side effects that developed during long-term exposure to a high dose of sildenafil.
Long-term mortality	The survival rate of patients during three years of treatment with sildenafil was comparable to that seen with other agents such as bosentan and epoprostenol.

VI.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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable for pre-approval versions.