Orisild 20 mg tablets

8.7.2016, Version 1.2

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

This medicinal product is used to treat adults, children and adolescents aged 1-17 years of age with pulmonary arterial hypertension (PAH, abnormally high blood pressure in the arteries of the lungs). In adults, sildenafil is used in patients with class-II (slight limitation of physical activity) or class-III (marked limitation of physical activity) PAH.

Pulmonary arterial hypertension is a rare debilitating lung disorder in which the arteries that carry blood from the heart to the lungs become severely narrowed, making it difficult for blood to flow through the vessels. As a result, the blood pressure in these arteries -- vessels taking blood from heart to lungs -- rises far above normal levels. This reduces the amount of oxygen that can get into the blood in the lungs, making physical activity more difficult.

If an underlying cause for the condition can't be found, the condition is called idiopathic pulmonary arterial hypertension. In most people with idiopathic pulmonary arterial hypertension, there is no recognized cause of the illness. However, some genes could be linked to disease. Therefore family history of pulmonary hypertension is a risk factor for this condition.

Pulmonary arterial hypertension that's consequence of some other medical problem is called secondary or associated pulmonary arterial hypertension. E.g. patients with HIV infection, systemic sclerosis or sickle cell disease have increased risk for development of pulmonary arterial hypertension.

Estimated prevalence of pulmonary arterial hypertension is 15-50 cases per million. Secondary pulmonary arterial hypertension is more common than idiopathic. Idiopathic pulmonary arterial hypertension has an annual incidence of 1-2 cases per million people in the US and Europe. Idiopathic pulmonary hypertension is 2-4 times as common in women as in men. The mean age at diagnosis is around 45 years, although the onset of symptoms can occur at any age. Older adults are more likely to have secondary pulmonary hypertension, and young people are more likely to have idiopathic pulmonary hypertension.

VI.2.2 Summary of treatment benefits

The active substance in this medicinal product, sildenafil, belongs to a group of medicines called ‘phosphodiesterase-type-5 (PDE5) inhibitors’, which means that it blocks the PDE5 enzyme. This enzyme is found in the blood vessels of the lungs. When it is blocked, a substance called ‘cyclic guanine monophosphate’ (cGMP) cannot be broken down, so that it remains in the vessels where it causes relaxation and widening of the blood vessels. In patients with pulmonary arterial hypertension, sildenafil widens the blood vessels of the lungs, which lowers the blood pressure and improves symptoms.

According to the studies made with originator product, Revatio, sildenafil was more effective than placebo at improving exercise capacity. Before treatment, adults with class-II disease could walk an average of 379 meter in six minutes. After 12 weeks, this distance had increased by 49 meters more in the patients taking 20 mg sildenafil than in the patients taking placebo. Adults with class-III disease could walk an

average of 325 meters at the start of the study. This distance had increased by 45 meters more in patients taking 20 mg sildenafil than in patients taking placebo after 12 weeks. As the three doses of sildenafil had similar effects, the lowest dose (20 mg three times a day) was chosen for use in adults.

In the study in children, the maximum volume of oxygen the patients used during exercise increased by 10.2% on average after 16 weeks of sildenafil treatment, while it increased by 0.5% on average for patients given placebo. The medium dose showed the best results.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of sildenafil in children below 1 year of age has not been established.

The efficacy of sildenafil has not been established in patients with severe pulmonary arterial hypertension (functional class IV).

The benefit-risk balance of sildenafil has not been established in patients assessed to be at WHO functional class I pulmonary arterial hypertension.

Studies with sildenafil have been performed in forms of pulmonary arterial hypertension related to primary (idiopathic), connective tissue disease associated or congenital heart disease associated forms of pulmonary arterial hypertension. The use of sildenafil in other forms of PAH is not recommended.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Interaction with medicines containing nitrates (Nitrate interaction)	Nitrates are a group of medicines used to treat angina pectoris. Concomitant administration of sildenafil and nitrates may result in dangerous drop in blood pressure.	Nitrates and sildenafil must not be used concomitantly.
Painful condition that develops when sickle-shaped red blood cells block blood flow through tiny blood vessels in patients with sickle-cell anemia (Vasoocclusive crisis in patients with sickle cell disease)	Periodic episodes of pain, called crises, are a major symptom of sickle cell anemia. Pain develops when sickle-shaped red blood cells block blood flow through tiny blood vessels to chest, abdomen and joints. Pain can also occur in bones. The pain may vary in intensity and can last for a few hours to a few weeks. In a clinical study events of vaso-occlusive crises requiring hospitalisation were reported more commonly by patients	Sildenafil should not be used in patients with pulmonary hypertension secondary to sickle cell anaemia.

Risk	What is known	Preventability
	receiving sildenafil than those receiving placebo.	
Increased relative risk of death in children (Increased relative mortality in the paediatric population)	A relative increase in deaths has been observed in children when higher than the recommended doses were administered.	Higher than recommended doses must not be used in children.
Nose bleed (Epistaxis)/bleeding events	Sildenafil can affect platelet aggregation and increase risk for nose bleed or other kind bleeding events. In pulmonary arterial hypertension patients, there may be a potential for increased risk of bleeding when sildenafil is initiated in patients already using a Vitamin K antagonist (e.g. warfarin), particularly in patients with pulmonary arterial hypertension secondary to connective tissue disease.	There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Very low blood pressure (Hypotension)	Sildenafil can have mild to moderate widening effect on blood vessels, which has blood pressure lowering effect. Sildenafil must not be used in patients with very low blood pressure. Careful benefit-risk assessment is necessary when treating patients for whom drop in blood pressure may cause problems. Caution should be administered in concomitant use with other medicines that can lower blood pressure.
Loss of vision because of a problem with blood flow to the nerve in the eye called non-arteritic anterior ischaemic optic neuropathy (NAION)	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 medicines belonging to the same group (PDE-5 inhibitors). Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION) must not use sildenafil. In the event of any sudden visual defect appear during treatment, use of sildenafil should be stopped immediately and alternative treatment should be considered.
Hearing loss	Sudden hearing loss has been reported in association with sildenafil therapy. Doctor should be informed of any previous hearing problems before sildenafil therapy is started. If symptoms appear

Risk	What is known (Including reason why it is considered a potential risk)
	during the treatment, doctor should be contacted.
Bleeding into the lungs in child patients (Pulmonary haemorrhage in paediatric population)	Pulmonary hypertension as such can lead to bleeding into the lungs and coughing up blood. In addition sildenafil can affect platelet aggregation and increase risk for nose bleed or other kind bleeding events.
Identified and potential interactions	
Identified interaction with bosentan (medicine to certain types of pulmonary arterial hypertension)	The efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated. In clinical study 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.
Potential interactions with epoprostenol and iloprost (medicines for pulmonary hypertension), other PDE5 inhibitors (medicines for erectile dysfunction including Viagra), alpha blockers (medicines for benign prostatic hyperplasia or high blood pressure)	Co-administration of oral sildenafil and intravenous epoprostenol has been evaluated. The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg, ambrisentan, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration. The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products, including Viagra, has not been studied in pulmonary arterial hypertension patients and such concomitant use is not recommended. Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the co-administration may lead to symptomatic hypotension in susceptible individuals. In order to minimise the potential for developing postural hypotension (drop in blood pressure when standing up), patients should stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms (e.g. dizziness, fainting).

Missing information

Risk	What is known
Long-term eye (ocular) safety	When used to treat male erectile dysfunction, the following visual side effects have been reported with PDE-5 inhibitors, including sildenafil at an unknown frequency; partial, sudden, temporary, or permanent decrease or loss of vision in one or both eyes. In addition bleeding at the back of the eye, effects on vision, blurred vision and light sensitivity, effects on colour vision, eye irritation, bloodshot eyes /red eyes, reduced sharpness of vision, double vision, abnormal sensation in the eye have been reported.
Safety in pregnancy	There are no data from the use of sildenafil in pregnant women.

Risk	What is known
	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. Due to lack of data, sildenafil should not be used in pregnant women unless strictly necessary.
Safety in patients with impaired kidney function (renal impairment)	Initial dose adjustments are not required in patients with renal impairment, including severe renal impairment. A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.
Safety in patients with heart and blood vessel (cardiovascular) diseases	The safety of sildenafil has not been studied in patients with recent history of stroke or heart-attack. In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular Events have been reported in temporal association with the use of sildenafil. 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 sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.
Long-term risk of death (mortality)	The effect of sildenafil on mortality is unknown. A total of 207 patients were treated with sildenafil in a clinical study, and their long term survival status was assessed for a minimum of 3 years.

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 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 this medicinal product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

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

Not applicable.