Important potential risks		
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	Wording and contraindication included in section 4.3 Warning in section 4.4 Listed in section 4.8	None proposed
Sudden Hearing Loss	Listed in section 4.8	None proposed
For women with PAH: Increased Uterine Bleeding (including menorrhagia, metrorrhagia, menometrorrhagia and vaginal haemorrhage)	Listed in section 4.8	None proposed
Missing information		
Characterization of adverse events in elderly patients (≥65 years)	Posology in section 4.2 Included wording in section 5.2	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

This medicine is used to treat adult men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.
Approximately 5-20% of men have moderate-to-severe erectile dysfunction. Various chronic disorders are associated with elevated rates of erectile dysfunction including depression, diabtes and cardiovasclar and neurological diseases. Such disorders are more common in the the elderly, which may partially explain the elevated prevalence of erectile dysfunction in men over 60 years of age. Besides, other parameters including peceived health, social status and other diagnosed conditions can result in erectile dysfunction.

This medicine is also used to treat adult men with urinary symptoms associated with a common condition called benign prostatic hyperplasia. This is when the prostate gland gets bigger with age. Symptoms include difficulty in starting to pass water, a feeling of not completely emptying the bladder and a more frequent need to pass water even at night. It is the most frequent urological problem in ageing men. It is estimated that approximatelly 40% of men by age of 50 and 80 % of men by the 80 years will have benign prostatic hyperplasia.

This medicine is also used to treat pulmonary arterial hypertension in adults. Pulmonary arterial hypertension is subgroup of pulmonary hypertension. Pulmonary hypertension is a pathophysiological disorder that may involve multiple clinical conditions and can complicate the majority of respiratory diseases. The World Health Organization (WHO) divides pulmonary hypertension into five groups, based on the cause of the condition. Pulmonary artery hypertension is a relatively rare chronic condition, which is, however, debilitating and can have a significant impact on quality of life. The lowest estimate of the prevalence of PAH

and idiopathic PAH is 15 cases per million in adult population. The lowest estimate of PAH incidence is 2.4 cases per million adult population per year. In Europe, PAH prevalence and incidence are in the range of 15 – 60 subjects per million population and 5 – 10 cases per million per year, respectively. In registries, around half of PAH patients have idiopathic, heritable or drug-induced PAH.

VI.2.2 Summary of treatment benefits

Tadalafil has been extensively investigated in well-designed, placebo-controlled clinical studies in patients with erectile dysfunction, benign prostatic hyperplasia and pulmonary hypertension.

Tadalafil has been proven as effective in treatment of erectile dysfunction across all severities and etiologies of the disease. Its efficacy has been proven in several clinical trials, and it is effective not only in the general erectile dysfunction population, but also the difficult-to-treat erectile dysfunction population with more severe erectile dysfunction and a greater number of comorbidities. Taken on-demand or once-daily, tadalafil significantly enhances erectile function. Once-daily dosing disconnects the temporal association of dosing a medication prior to the sexual encounter. Furthermore, tadalafil was well tolerated across all administered doses.
Several studies also investigated efficacy of 5 mg tadalfil for the treatment of benign prostatic hyperplasia and its symptoms. The efficacy of tadalafil was established from placebo-controlled studies. In study with 427 men included the long-term efficacy of tadalafil was evaluated. In this study it was concluded that the efficacy of tadalafil is maintained for at least 1 year.

The clinical program investigating tadalafil for treatment of pulmonary arterial hypertension has been less extensive, however the included patients demonstrated significantly improved exercise capacity as measured by the 6-minute walk distance. Patients also experienced decreased incidence of clinical worsening, increased quality of life, and improved cardiopulmonary hemodynamics. Uncontrolled studies and smaller trials have indicated a possible role for tadalafil as a suitable alternative to sildenafil and as a beneficial add-on option when used in combination with other treatments for pulmonary arterial hypertension.

VI.2.3 Unknowns relating to treatment benefits

There are limited data in clinical studies for patients over 65 years of age.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Prolonged erection of penis (Priapsm)	In some cases prolonged (lasting more than 4 hours) and possibly painful erection after taking tadalafil is possible. Patients with anatomical deformation of the penis or	The doctor or pharmacist should be informed if the patient has any deformation of penis, or unwanted or persistent erections lasting more than 4 hours or any condition which can predispose

	patients with abnormality of red blood cells (sickle cell anaemia), cancer of the bone marrow (multiple myeloma) or cancer of the white blood cells (leukaemia) are at increased risk experiencing such condition.	prolonged erection.
Low blood pressure (Hypotension/Increased Hypotensive Effect)	The use of tadalafil may lead to low blood pressure. This is more common in patients who are taking nitrates and riociguat (medicine to treat pulmonary hypertension or chronic thromboembolic pulmonary hypertension), as tadalafil increases the hypotensive (blood pressure-lowering) effect of these medicines. Tadalafil also potentiates the effect of medicines used to treat high blood pressure (anti-hypertensives), leading to an increased reduction in blood pressure (increased hypotensive effect). Drinking alcohol may as well temporarily lower blood pressure.	The doctor or pharmacist should be informed if the patient is taking any form of organic nitrate or nitric oxide donors such as amyl nitrite or riociguat as these medicines have been shown to increase the hypotensive effects of tadalfil. The doctor or pharmacist should be informed if patient is taking other medicines to treat high blood pressure because co-administration may increase the blood pressure-lowering effect of such medicines.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Nonarteric Anterior Ischemic Optic Neuropathy (NAION)	Visual defects and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Patients should not take medicine if they ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye.
Sudden Hearing Loss	In some cases loss of hearing is possible. Patient should contact doctor imediatelly if experience such ADR .
For women with PAH: Increased Uterine Bleeding (including menorrhagia, metrorrhagia, menometrorrhagia and	It is possible that female patient experience increased or abnormal uterine bleeding when treated with tadalafil for pulmonary artery hypertension. Patient should contact doctor imediatelly if experience such

vaginal haemorrhage)	ADRs.

Missing information

Risk	**What is known**
Use in older patients (≥65 years)	There are limited data about usage of tadalfin in elderly.

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 product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.