VI.2   Elements for a Public Summary

VI.2.1   Overview of disease epidemiology

Erectile dysfunction

Erectile dysfunction (ED) is a very prevalent problem in men worldwide. The condition increases with age and is found in more than 50% of men older than the age of 65-70 years in most studies. This problem is complex and involves multiple pathways. A variety of medical conditions are associated with an increased risk of ED, including diabetes, vascular disease, and depression, as well as elevated cholesterol levels, arthritis, hypertension, and heart disease. Diseases that impair penile blood flow or innervation will most likely have pathophysiological links to ED, whereas diseases that lower a man's sense of well-being may impair libido and mood, leading to secondary reduction in erectile function6. ED can be psychogenic, organic or a mix of both. Psychological and sexological management can help some patients suffering from psychogenic ED. Although the disorder is common and frequently underdiagnosed, its treatment can significantly improve patients' quality of life7.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a common disease among older men and is the most common form of prostate disease, accounting for over 80% of clinical presentations[8]. It is also the most common cause of lower urinary tract symptoms (LUTS) in elderly men. Therefore, although LUTS may be caused by other diagnoses (e.g., prostatitis, urinary stones, prostate cancer or bladder cancer), studies of the prevalence of LUTS are a good indication of the prevalence of BPH in this population. The 2003 UrEpik study[9] of LUTS, using the International Prostate Symptom Score (IPSS) in men aged 40-79 years, found that the prevalence of LUTS was remarkably similar across all four centres (three in Europe and one in Korea) of the study. Prevalence of the condition increases with age, with it affecting almost 20% of 50-59 year olds, 30% of 60-69 year olds and 40% of 70-79 year olds. In terms of BPH, the figures for the 60-69 year olds and 70-79 year olds are the most relevant. These figures represent a considerable symptom burden, which will be magnified by the ageing population effect.

VI.2.2   Summary of treatment benefits

Erectile dysfunction

The MAH has provided ten clinical trials10-19, four meta-analyses20-23 and two reviews of clinical trials24,25 to evaluate the efficacy and safety of tadalafil in adult men suffering ED. In placebo-controlled clinical trials, tadalafil

demonstrated significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing. The results of analyses from pooled clinical trials show that tadalafil patients had significantly higher first-attempt success rates compared with placebo, with a marginally better effect of the 20 mg dose. Tadalafil administered to healthy subjects produced no significant difference compared to placebo in blood pressure and in heart rate.

Benign prostatic hyperplasia

Tadalafil given at a dose of 5 mg is more effective than placebo in the studies in patients with BPH, with the results showing a significant improvement of symptoms compared with placebo. The MAH provides one clinical trial[26] and three meta-analyses[27-29] to evaluate the efficacy and

safety of tadalafil in men with BPH. The clinical trial[26] revealed that tadalafil 5 mg once daily improved LUTS associated with BPH in men without ED by a magnitude similar to that observed in men with ED. Meta-analyses showed good efficacy and safety of tadalafil for improving LUTS and erectile function in men with BPH. No significant difference with placebo was detected in the incidence of serious adverse events after tadalafil treatment.

VI.2.3 Unknowns relating to treatment benefits

Data in patients over 65 years of age receiving tadalafil in clinical studies, either for the treatment of ED or the treatment of BPH, are limited. Data show that more patients over 75 years of age treated with tadalafil had dizziness than younger patients, and that diarrhoea has been reported more frequently in men over 65 years of age taking tadalafil on demand for the treatment of erectile dysfunction. Given that elderly patients constitute an important target population, the need to generate more data in this population has been included as missing information in this Risk Management Plan.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Prolonged and possible painful erection (priapism)	In rare cases, the treatment with tadalafil may lead to a prolonged (lasting 4 hours or more) and possibly painful erection. This risk is more common in patients with anatomical deformations of the penis or in those who have conditions which may predispose them to suffer prolonged and possibly painful erections, such as an abnormality of the red blood cells called sickle cell anaemia, cancer of the bone marrow (multiple myeloma) or cancer of the white blood cells (leukaemia). If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.	Patients should inform their doctor if they have cancer of the bone marrow or cancer of the blood white cells, an abnormality of the red blood cells or any deformation in the penis. Tadalafil should be used with caution in these patients. If a patient experience a possible painful erection which lasts continuously for more than 4 hours, he should contact a doctor immediately.
Blood pressure decreased (hypotension/increased	The use of tadalafil may uncommonly lead to low blood pressure. This effect is more common in patients receiving nitrates (medicines used in	Patients should not take tadalafil if they are receiving concomitant nitrates. Patients should inform

Risk	What is known	Preventability
hypotensive effect)	the treatment of angina pectoris -"chest pain"-), as tadalafil has been shown to increase the hypotensive (blood pressure-lowering) effects of these drugs. Tadalafil also potentiates the hypotensive effects of riociguat, a medicine used for the treatment of the pulmonary arterial hypertension (high blood pressure in the lungs) and the medicines used to treat high blood pressure (antihypertensive medicinal products), leading to an increased reduction in blood pressure (an increased hypotensive effect). Blood pressure may temporarily decrease with the concomitant use of alcohol.	their doctor if they are receiving an alpha blocker (used to treat high blood pressure or urinary symptoms associated with benign prostatic hyperplasia), other medicines to treat high blood pressure, riociguat, and a 5-alpha reductase inhibitor (used to treat benign prostatic hyperplasia). Drinking alcohol may temporarily lower blood pressure. If patient have taken or is planning to take tadalafil, should avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up. The patient should tell his doctor if he has low blood pressure or uncontrolled high blood pressure.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Stroke of the eye (non-arteritic anterior ischemic optic neuropathy (NAION))	Partial, temporary, or permanent decrease or loss of vision in one or both eyes has been rarely reported in patients receiving tadalafil. This condition is known as NAION and is described as "stroke of the eye". Patients should inform their doctor if they ever had loss of vision because of NAION ("stroke of the eye"). If patients experience sudden decrease or loss of vision while taking tadalafil, they should stop taking this medicine and contact their doctor immediately.
Sudden hearing loss	In rare cases, patients receiving tadalafil may experience a sudden decrease or loss of hearing.

Missing information

Risk	What is known
Use in older patients (characterisation of adverse events in elderly patients (≥65 years))	In the currently small sample size data available, it has been shown that the side effect dizziness has been reported more frequently in men over 75 years of age taking tadalafil, compared to patients below 75 years of age, and that diarrhoea has been reported more frequently in men over 65 years of age taking tadalafil on demand for the treatment of erectile dysfunction. Although in general there were no important differences, these adverse reactions were more frequent in older patients.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists, and other HCPs with details on how to adequately use these medicines, identifies the risks and provides recommendations for minimising risks. An abbreviated version of this in lay language is provided in the form of the PL. The measures described in the SmPC and PL are known as Routine Minimisation Measures.

The SmPC and the PL for Tadalafil Farmaprojects 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets are available.

These medicines have no additional risk minimisation measures.

VI.2.6 **Planned post authorisation development plan**

Farmaprojects S.A.U. does not plan to further investigate the safety and efficacy of tadalafil-containing medicinal products. Farmaprojects S.A.U. will closely monitor all safety concerns using routine pharmacovigilance activities.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	16-Aug-2016	-	Implementation of issues to be addressed from the preliminary Assessment Report dated 17 May 2016. Implementation of the scientific conclusions and grounds for the variation to the terms of the marketing authorisation for tadalafil (Procedure Nº EMEA/H/C/PSUSA/00002841/2015 10) dated 26 May 2016