

## 4.2 Part VI.2 Elements for a Public Summary

### 4.2.1 Part VI.2.1 Overview of disease epidemiology

Tadalafil is used in the treatment of erectile dysfunction ([ED] inability to develop or maintain an erection of the penis during sexual activity), benign prostatic hyperplasia ([BPH] non-cancerous enlargement of the prostate gland) and pulmonary arterial hypertension (abnormal constriction of blood vessels supplies blood to lungs which increases blood pressure within lungs) in adults.

#### Erectile Dysfunction in adult males

ED or impotence is defined by a National Institutes of Health consensus panel as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. Worldwide estimates of ED occurrence range from 2% in men younger than 40 years to 86% in men 80 years or older. Risk factors for ED include aging, co-morbid disease, certain medications, obesity (overweight), and lifestyle behaviors (e.g., alcohol and tobacco use). The occurrence rates for mild and severe ED has been reported as 35% in the United States, 26% in Finland, 21% in Italy, 12% in France, and 11% in Spain. [[Shabsigh, 2006](#)].

#### Benign Prostatic Hyperplasia

BPH is a common, non-cancerous enlargement of the prostate gland. The enlarged prostate may compress the urethra (urinary tube), which courses through the center of the prostate, interrupting the flow of urine from the bladder through the urethra to the outside. BPH develops as a strictly age-related phenomenon in nearly all men, starting at approximately 40 years of age. In fact, the histological occurrence of BPH, which has been examined in several autopsy (post-mortem examination) studies around the world, is approximately 10% for men in their 30s, 20% for men in their 40s, reaches 50% to 60% for men in their 60s, and is 80% to 90% for men in their 70s and 80s. No doubt, when living long enough, most men will develop some histologic features consistent with BPH. [[Roehrborn CG.,2005](#)].

#### Pulmonary Arterial Hypertension (PAH)

PAH is a condition where in the pulmonary arteries constrict abnormally which forces your heart to work faster and causes increase in blood pressure within the lungs. Studies have provided low estimates of category 1 PAH (type of disease) occurrence of 15 cases/million of adult population and frequency of 2.4 cases/million of adult population/year in France [[Humbert M, 2006](#)] and in United States it is estimated to be 10.6 and 2.0 respectively [[Frost AE, 2011](#)]. The mean age was 36 years in patients entered into the 1980's National Institutes of Health registry, with a female to male ratio of 1.7 [[Rich S, 1987](#)].

### 4.2.2 Part VI.2.2 Summary of treatment benefits

Tadalafil is used in the treatment of ED, BPH and PAH in adults.

PDE5 inhibitors, the group of drugs to which tadalafil belongs, are the current first-line treatment option for the majority of men with ED due to their known efficacy and safety profile [[Konstantinos, 2014](#)]. Tadalafil has also been shown to be an effective treatment for more severe, organic ED evaluated in tertiary care centers (hospitals), ED secondary to diabetes mellitus and ED resulting from prostate cancer treatments such as prostatectomy (surgical removal of all or part of the prostate gland) and radiotherapy (treatment for cancer using high energy radiation) [[Coward RM, 2008](#)].

ED and BPH associated lower urinary tract symptoms (LUTS) share common pathophysiological pathways (study of changes in the way the body works resulting from disease). Tadalafil 5 mg once daily is approved for the treatment of BPH associated LUTS in men with or without ED. In addition to these facts, tadalafil is an established treatment for ED and is the only drug available that can treat simultaneously two conditions that are highly common in aging men. The combination of tadalafil 5 mg and finasteride 5 mg improved BPH significantly compared with finasteride monotherapy along with a significant improvement in ED [[Konstantinos, 2014](#)].

In the treatment of PAH (including idiopathic [unknown cause] and associated) tadalafil 40 mg, significantly improved exercise capacity, clinical worsening, quality of life, and hemodynamics (continuous monitoring of blood flow and pressure being exerted in the blood vessels and heart chambers) in patients who had symptoms in WHO functional class II or III PAH, and had idiopathic PAH or associated PAH (connective tissue disease [group of disorders involving the protein-rich tissue that supports organs and other parts of the body], HIV infection, or congenital systemic-to-pulmonary shunts [birth defect resulting in increase blood pressure in lungs]) [\[Galie N, 2009\]](#).

#### 4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of tadalafil with regards to the treatment of PAH in individuals below 18 years of age has not yet been established. The efficacy of tadalafil when co-administered with prostacyclin or its analogues has not been studied, therefore, caution is recommended in case of co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated. It is not known if tadalafil is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

#### 4.2.4 Part VI.2.4 Summary of safety concerns

**Table 4-5 Important identified risks**

Risk	What is known	Preventability
Persistent and painful erection of the penis (Priapism)	Patients can experience painful erections lasting for more than 4 hours. If not treated immediately it may cause tissue damage and permanent loss of potency	Patients who experience - prolonged and possibly painful erections lasting continuously for more than 4 hours should be instructed to seek immediate medical assistance. Before taking the medication, the doctor should be informed if patient had any deformation of the penis, or unwanted or persistent erections lasting more than 4 hours.
Significant decrease in blood pressure (Hypotension/ Increased hypotensive effect)	The use of tadalafil can decrease the blood pressure significantly.	Patients should be advised to tell the doctor if they experience symptoms of low blood pressure. Additionally patients should be advised to not take medicines which could lower the blood pressure, too.

**Table 4-6 Important potential risks**

Risk	What is known
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Sudden hearing loss	Sudden decrease in hearing or loss of hearing can occur.
Impairment of vision or blockage in the blood vessels in your retina (NAION)	Loss of vision can occur due to stroke of the eye or visual defects can occur. Patient should be advised to not to take the medicine if have ever had loss of vision. Before starting the medication, patient should inform to doctor if had any hereditary eye disease and should consult doctor immediately if had experienced sudden decrease or loss of vision.
More blood could come out of the womb (increased uterine bleeding)	Includes abnormal/excessive menstrual bleeding conditions (such as menorrhagia, metrorrhagia, menometrorrhagia, or vaginal hemorrhage), common

**Table 4-7 Missing Information**

Missing information	What is known
The information on side effects of tadalafil in people elder than 65 years of age is limited (Characterization of adverse events in elderly (over 65 years of age))	Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhea was reported more frequently in patients over 65 years of age. In clinical trials with tadalafil 5 mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhea were reported more frequently in patients over 75 years of age.

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

None

**4.2.6 Part VI.2.6 Planned post authorization development plan**

None

**4.2.6.1 List of studies in post authorization development plan**

None

**4.2.6.2 Studies which are a condition of the marketing authorization**

None

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

Not applicable (first submission)