

**VI.2 Elements for a public summary****VI.2.1 Overview of disease epidemiology****Erectile dysfunction (ED)**

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED is a highly prevalent condition among men all over the world. It has a significant negative impact on the quality of life of the patients and their partners. Its prevalence and incidence are associated with aging as well as important co-morbidities, such as heart diseases, diabetes (high blood sugar level), combination of the medical disorder that leads to heart disease and diabetes (metabolic syndrome), increase cholesterol level in blood (hyperlipidemia), depression, side effects of medications, neurological disorders, trauma, and psychological and interpersonal problems. Furthermore, lifestyle choices of major public health impact are also associated with ED. These include preventable causes of disease such as obesity, smoking, alcohol abuse, and sedentary lifestyle

**Benign Prostatic Hypertrophy**

Benign prostatic hyperplasia is a common condition with advancing age; it results in enlargement of the prostate, which may restrict the flow of urine from the bladder. It is an increase in size of the prostate gland without malignancy present and it is so common as to be normal with advancing age. BPH affects the quality of life of about 40% of men in their fifth decade and 90% of men in their ninth decade. It is unusual before the age of 45 and affects men of Afro-American origin more severely than white men, possibly due to higher hormone levels. BPH is a common problem that affects the quality of life in approximately one third of men older than 50 years. BPH is evident in up to 90% of men by age 85 years. Worldwide, approximately 30 million men have symptoms related to BPH.

**Pulmonary Arterial Hypertension (PAH)**

Pulmonary hypertension is high blood pressure in the arteries going to the lung. If the pulmonary artery pressure exceeds about 40/20 mm Hg or the average pressure exceeds 25 mm Hg, then pulmonary hypertension is present. Since the late 1990s, there has been

increasing interest in the causes, consequences and treatment of PAH. The exact data regarding occurrence of pulmonary arterial hypertension is not available. According to the data published by registry suggested approximately 2-8 cases reported per million populations, in which 1-2 cases per million populations were reported for the pulmonary arterial hypertension with unknown cause. As per registry, the occurrence of pulmonary arterial hypertension in Czech Republic is around 10-11 cases per million population in 2007.

### **VI.2.2 Summary of treatment benefits**

For the treatment of erectile dysfunction, tadalafil has been investigated in six main studies involving 1,328 patients, in which the medicine was taken 'on demand' before sexual activity, and in 3 other studies involving 853 patients in which tadalafil was taken once a day. In all studies, the effects of tadalafil were compared with those of placebo (a dummy treatment), and the main measure of effectiveness was the ability to get and maintain an erection.

Tadalafil was found to be significantly more effective than placebo at treating erectile dysfunction. Overall, in the studies of general populations, 81% of patients reported that tadalafil 'on demand' improved their erections as compared to 35% of those taking placebo. Patients taking tadalafil once a day at doses of 2.5 or 5 mg also reported improved erections compared with those taking placebo.

For the treatment of benign prostatic hyperplasia, tadalafil was studied in 4 studies in over 1,500 patients. Tadalafil given at a dose of 5 mg was more effective than placebo, with the results showing a significant improvement in symptoms after 12 weeks. The maintenance of the effect was evaluated in one of the studies, which showed that the improvement in total international prostate symptom score seen at 12 weeks was maintained for up to 1 additional year of treatment with tadalafil 5 mg.

**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 erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. There are also no available data about the administration of tadalafil doses higher than 10 mg to patients with liver impairment.

**VI.2.4 Summary of safety concerns**

**Important identified risks:**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Prolonged and painful erection (Priapism)	Prolonged and painful erection is a rare side effect which may affect more than 1 in 10,000 to less than 1 in 1000 people.	Yes  Before taking the tablets, the patient should inform their doctor if they have any deformation of their penis or unwanted or persistent erections lasting more than 4 hours.  If the patients have such an erection, which lasts continuously for more than 4 hours, the patient should contact a doctor immediately.
Low blood pressure (hypotension / increased hypotensive)	Low blood pressure is an uncommon side effect which may affects up to 1 in 100 people.	Yes  The patient should tell their doctor or pharmacist

<p>effect)</p>		<p>if they are already taking other medicines to treat high blood pressure.</p> <p>The patient should not take Accord tadalafil, if they have low blood pressure or uncontrolled high blood pressure.</p>
<p>Serious cardiovascular events (serious events related to heart and blood vessels)</p>	<p>Pounding heartbeat sensation, fast heart rates are uncommon side effects which may affect up to 1 in 100 people.</p> <p>Heart attack and stroke have also been reported rarely in men taking tadalafil. Most of these men had known heart problems before taking this medicine.</p> <p>For an indication of pulmonary arterial hypertension (20 mg):</p> <p>Fast heart rate is an uncommon side effect.</p> <p>Most but not all of those men reporting fast heart rate, irregular heartbeat, heart attack, stroke (brain attack) and sudden cardiac death had known heart problems before taking tadalafil. It is not possible to determine whether these events were</p>	<p>Yes</p> <p>Before taking the tablets, the patient should tell his doctor if he have any heart problems other than pulmonary hypertension.</p> <p>The patient should be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on their heart.</p>

	related directly to tadalafil.	
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**Important potential risks**

<b>Risk</b>	<b>What is known</b>
Non-arteritic anterior ischaemic optic neuropathy (NAION) {Sudden loss of vision in one or both eye due to lack of blood supply to eye	<p>Partial, temporary, or permanent decrease or loss of vision in one or both eyes has been rarely reported.</p> <p>Some additional rare side effects have been reported in men taking tadalafil that were not seen in clinical trials. These include some disorders affecting blood flow to the eyes.</p> <p>The patients should not take tadalafil if they ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.</p> <p>Before taking the tablets, the patients should tell their doctor if they have -any hereditary eye disease.</p>
Sudden hearing loss	<p>Sudden decrease or loss of hearing is a rare side effect.</p> <p>If the patient experience sudden decrease or loss of hearing, they should stop using the medicine and seek medical help immediately.</p>
Increased uterine bleeding (Increased bleeding in an organ where the unborn baby develops and grows)	<p>Increased bleeding in an organ where the unborn baby develops and grows is a common side effect which may affects more than 1 in 100 to less than 1 in 10 people.</p>
Medication errors	<p>In order to prevent medication error, strengths are available in different colour, size, shape and characters and</p>

<b>Risk</b>	<b>What is known</b>
	<p>additionally MAH has proposed separate product information (including patient information leaflet and summary of product characteristics) for the different strengths, with the respective indications to avoid confusion for healthcare professionals and patients.</p> <p>2.5 mg tablets are white, round, approximately 5.5 mm in diameter, biconvex, bevelled edged, and debossed with "T" on one side and "25" on other side.</p> <p>5 mg tablets are light yellow, capsule shaped, approximately 8.6 mm in length and 4.8 mm in width, biconvex, bevelled edged and debossed with "T 5" on one side and plain on other side.</p> <p>10 mg tablets are light yellow, capsule shaped, approximately 11 mm in length and 5.5 mm in width, biconvex, bevelled edged, and debossed with "T 10" on one side and plain on other side.</p> <p>20 mg tablets are yellow, capsule shaped, approximately 14.3 mm in length and 7 mm in width, biconvex, bevelled edged and debossed with "T 20" on one side and plain on other side.</p>

**Missing information**

<b>Risk</b>	<b>What is known</b>
Use in older patients ( $\geq 65$ years)	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.
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### VI.2.5 Summary of additional 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.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
3.0	19 February 2016	No change in safety concerns	RMP has been updated as per Day 120 & day 145 comments. Routine Risk Minimisation Measure for Important potential risk "Medication error" has been updated.
2.0	30-October-2015	Following safety concerns were added  Important potential risks:	RMP has been updated as per Day 70 and Day 100 comments.

<b>Version</b>	<b>Date</b>	<b>Safety Concern</b>	<b>Comment</b>
		<ul style="list-style-type: none"><li>• Increased uterine bleeding</li><li>• Medication errors</li></ul>	