13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Erectile dysfunction (ED) is defined by a consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity. ED has serious negative consequences on both sexual experience and emotional well - being and affects a broad range of age groups [1]. A review of ED prevalence (the proportion of a population found to have a condition) is less than 10% in men aged below 50, superior to 20% for men over 60. Age, cardiovascular diseases, diabetes, hypercholesterolemia, smoking, depression and psychiatric illness, psychological disorders, unfavorable socio-economic conditions are all risk factors for erectile dysfunction. Drug sexual side-effects must also be envisaged. Erectile dysfunction can be psychogenic, organic or a mix of both. The pathophysiological mechanisms are diverse and can implicate deterioration of the central or peripheral neural pathways, from the arterial supply to the penis, endothelial dysfunction, smooth muscle tone impairment, structural damage of the sinusoidal spaces of the erectile tissue, or even hormonal disorders.
Psychological and sexological management can help some patients suffering from psychogenic erectile dysfunction, usually associated with pharmacological treatment [3]. Although the disorder is common and underdiagnosed, its treatment can significantly improve patients' quality of life.[1]

13.2.2 Part VI.2.2 Summary of treatment benefits

Several studies, including four double-blind, placebo-controlled, Phase II trials, show that alprostadil topical cream is efficacious and well-tolerated in ED in patients with mild-to-severe symptoms, in those undergoing treatment for cardiovascular diseases and diabetes and in otherwise healthy ED patients. Alprostadil topical cream is a potential first-choice alternative for ED in patients who do not respond or who cannot tolerate or do not accept PDE-5 inhibitor therapy [1]. Topical alprostadil cream significantly improves ED in a broad range of patients. Most adverse events were limited to the application site and were generally well tolerated [4].

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The pharmacokinetics of Alprostadil has not been formally studied in patients with hepatic and /or renal insufficiency. The dose may need to be lowered in these populations due to impaired metabolism. Clinical studies have not been conducted in patients with a history of

neurological disease or spinal injury. In addition, patients with underlying disorders, such as orthostatic hypotension, myocardial infarction and syncope, should not use Alprostadil.
Patients with pulmonary disease may have a reduced capacity to clear the drug. In patients with adult respiratory distress syndrome, pulmonary extraction of intravenously administered PGE1 was reduced by approximately 15% compared to a control group of patients with normal respiratory function.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
Spermatotoxicity (toxic for the sperms)	Alprostadil has no effect on sperm count or morphology. However, the excipient DDAIP caused atrophy of the seminiferous tubules of the testes in rabbits when administered locally at a concentration of 5%. A direct spermatotoxic effect of DDAIP could not be tested, and the relevance for a possible reduced male fertility in humans is therefore unknown. DDAIP administered subcutaneously to rats had no effect on fertility.	Alprostadil should not be used if a pregnancy is planned. Talk to your doctor to discuss other treatment options of your ED (e.g. vacuum constriction device)
Hypotension; Dizziness; Syncope (fainting)	Dizziness and syncope have been reported rarely in clinical trials with Aprostadil. Symptomatic hypotension (dizziness) and syncope occurred in a small percent of patients (2/459 (0.4%), 6/1591 (0.4%), and 6/1280 (0.5%) at the 100, 200 and 300 mcg alprostadil doses, respectively, during dosing in the Phase 3 studies.	Alprostadil should not be used if you have underlying disorders such as orthostatic hypotension, mycardial infarction and syncope (dizziness). Avoid activities, such as driving or hazardous tasks, where injury could result if hypotension or syncope occurs after Alprostadil administration.
Priapism (an erection lasting longer than 4 hours)	Priapism, although rare, was observed with the use of Alprostadil.	If priapism occurs, seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.
Carcinogenicity (causing tumors)	Carcinogenicity studies with alprostadil have not been conducted. Carcinogenicity assessments of the excipient, DDAIP, found no tumor formation with topical administration to mice and subcutaneously in rats.	Not applicable

Table 13-6 Important potential risks

Risk	What is known
Embryotoxicity (toxic for the embryo)	Alprostadil has been shown to be embryotoxic (decreased foetal weight) when administered as a subcutaneous bolus to pregnant rats at low doses. Higher doses resulted in increased resorptions, reduced numbers of live foetuses, increased incidences of visceral and skeletal variation and malformations, and maternal toxicity. Intravaginal administration of PGE1 to pregnant rabbits resulted in no harm to the foetus. Reproductive toxicity studies for DDAIP were performed after subcutaneous administration to rats and rabbits. No effects were seen in rats, but in rabbits foetotoxicity including increased malformations were seen at high doses,whichwasprobablyduetomaternaltoxicity.
Use in patients with cardiovascular or unstable cerebrovascular conditions (problems with heart or brain vessels)	There is no clear indication that alprostadil increases the risk of cardiovascular events, other than the vasodilative effects, but it cannot be excluded that patients with underlying disease/risk factors are at increased risk in combination with increased sexual/physical activity that is associatedwithalprostadiluse.
Possible interaction with sildenafil or penile implants	The safety and efficacy for Alprostadil in combination with other treatments for erectile dysfunction, especially for the treatment with Phosphodiesterase-5 inhibitors (PDE-5) or sildenafil, tadalafil and vardenafil , has not been studied. No interaction studies have been performed for Alprostadil in combinationwithpenileimplants.
Urinary tract infection	Introduction of the dispenser into the opening of the penis will increase the risk of introducing infection; poor hygiene or not discarding the dispenser if all the product is not used, willincreasethisrisk.

Table 13-7 Missing information

Risk	What is known
Long term safety data for alprostadil	Long term safety data is not available.
Patients with a history of • Myocardial infarction • Neurological disease (stroke) • Spinal injury • Pulmonary disease	Clinical studies have not been conducted in patients with a history of neurological disease or spinal injury. Patients with pulmonary disease may have a reduced capacity to clear the drug. In patients with adult respiratory distress syndrome, pulmonary extraction of intravenously administered PGE1 was reduced by approximately 15% compared to a control group of patients with normal respiratoryfunction.

13.2.5 Part VI.2.5 Summary of additional risk minimization 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.

13.2.6 Part VI.2.6 Planned post authorization development plan

None

13.2.7 Part 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
1.0	25 Apr 2014	N/A	The Sandoz RMP version 1.0 is a copy of the License partner RMP v 2.0 dated 27 April 2012 which was approved in the procedure NL/H/2379/001-002/DC.