Summary of activities in the risk management plan

1 Elements for summary tables in the EPAR

1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Breast cancer in men
Important potential risks	Exposure in Pregnancy - risk to male foetus
Important missing information	Breastfeeding

1.2 Summary table of risk minimisation measures

Safety Concern	**Routine Risk Minimisation measures**	**Additional Risk Minimisation measures**
Breast cancer in men	• Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge mentioned in section 4.4 of SmPC. • Special warnings and precautions for use in section 4.4 of SmPC • Listed in section 4.8 of SmPC	Not applicable
Exposure in Pregnancy - risk to male foetus	• Mentioned in Fertility, pregnancy and lactation section 4.6 of SmPC • Mentioned in Contraindications section 4.3 of SmPC • Mentioned in Special precautions for disposal and other handling section 6.6 of SmPC	Not applicable
Breastfeeding	• Mentioned in Fertility, pregnancy and lactation section 4.6 of SmPC	Not applicable

2 Elements for a public summary

2.1 Overview of disease epidemiology (for each indication)

Indication/target population	**Benign prostatic hyperplasia (BPH)**
Incidence and prevalence	Globally, benign prostatic hyperplasia (BPH) affects about 210 million males as of 2010 (6% of the population). The prostate gets larger in most men as they get older. For a symptom-free man of 46 years, the risk of developing

	BPH over the next 30 years is 45%. Incidence rates increase from 3 cases per 1000 man-years at age 45–49 years, to 38 cases per 1000 man-years by the age of 75–79 years. While the prevalence rate is 2.7% for men aged 45–49, it increases to 24% by the age of 80 years. A large European analysis of family physician records found an overall prevalence of lower urinary tract symptoms (LUTS) suggestive of the incidence of BPH being 10.3% in men older than 45, which increased to 24% at age 80. BPH is the most common benign neoplasm in males. Autopsy studies estimate that 40% of men in their 50s, 70% in their 60s and 88% in their 80s will have evidence of BPH. In the USA, results of the Olmstead County survey, in a sample of unselected Caucasian men aged 40-79 years, showed that moderate-to-severe symptoms can occur among 13% of men aged 40-49 years and among 28% of those older than 70 years. In Canada, 23% of the cohort studied presented with moderate-to-severe symptoms. The findings for prevalence of LUTS in Europe are similar to those in the USA. In Scotland and in the area of Maastricht, the Netherlands, the prevalence of symptoms increased from 14% of men in their 40s to 43% in their 60s. Depending on the sample, the prevalence of moderate-to-severe symptoms varies from 14% in France to 30% in the Netherlands.
Demographics of the target population – age, sex, race/ethnic origin	Increasing age, Black men appear to have a higher risk and Asian men have a lower risk.
Risk factors for the disease	BPH can be seen in the vast majority of men as they age and intact androgen supply seems to be prerequisites for BPH development.
Main treatment options	Benign prostatic hyperplasia (BPH) cannot be cured, so treatment focuses on reducing your symptoms • Watchful waiting may be your best treatment. With this treatment, you may make small changes to your lifestyle to control your symptoms, but you do not take medicines or have surgery. • If possible, avoid medicines that make your symptoms worse. • Spread your fluid intake throughout the day. Limit fluid intake in the evening if you frequently awaken at night to urinate.

	• You may want to try an herbal therapy for BPH, such as saw palmetto or beta-sitosterol. Talk with your doctor before starting any herbal therapy.
Mortality and morbidity (natural history)	BPH-associated mortality is rare in the United States, and serious complications are uncommon.

Indication/target population	**Treatment of the first stage of the hair loss (androgenetic alopecia) in males.**
Incidence and prevalence	An estimated 30% of men developed androgenetic alopecia by the age of 30 and 50% by the age of 50.[10] Androgenetic alopecia is an extremely common disorder that affects roughly 50% of men. A community-based study of androgenetic alopecia in 6 cities in China indicated that the prevalence of androgenetic alopecia in both Chinese males and females was lower than that seen in whites but similar to the incidence among Koreans. The prevalence of vertex or full baldness increase with age from 31% (age 40–55) to 53% (age 65–69). A receding frontal hairline was found in 25% of men aged 40–55 and 31% aged 65–69.
Demographics of the target population – age, sex, race/ethnic origin	Almost all patients with androgenetic alopecia have an onset prior to age 40 years, although many of the patients (both male and female) show evidence of the disorder by age 30 years. The incidence and the severity of androgenetic alopecia tend to be highest in white men, second highest in Asians and African Americans, and lowest in Native Americans and Eskimos.
Risk factors for the disease	The inheritance pattern of androgenetic alopecia is unclear because many genetic and environmental factors are likely to be involved. This condition tends to cluster in families, however, and having a close relative with patterned hair loss appears to be a risk factor for developing the condition. Hereditary baldness, Consumption of alcohol and lean body mass at age 21 years.

Main treatment options	Only 2 medications have been shown to be effective in the treatment of androgenetic alopecia: minoxidil and finasteride. Minoxidil is applied topically and available as 2% or 5% solutions. Finasteride is taken orally.
Mortality and morbidity (natural history)	Androgenetic alopecia is significant only in that it allows ultraviolet light to reach the scalp and, thus, increases the amount of actinic damage. Males with androgenetic alopecia may have an increased incidence of myocardial infarction. An increase in benign prostatic hypertrophy has also been associated with androgenetic alopecia. A study found that men with higher grades of androgenetic alopecia (vertex balding) have a higher risk of developing ischaemic heart disease, especially among men with hypertension or high cholesterol levels.

2.2 Summary of treatment benefits

Finasteride is a synthetic drug approved by the FDA for the treatment of benign prostatic hyperplasia (BPH) and male pattern baldness (MPB). It is a type II 5α-reductase inhibitor [5-Alpha-Reductase Inhibitor (5ARI)]. 5α-reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT).

Finasteride, a 4-azasteroid and analogue of testosterone, works by acting as a potent and specific, competitive inhibitor of one of the two subtypes of 5α-reductase, specifically the type II isoenzyme. In other words, it binds to the enzyme and prevents endogenous substrates such as testosterone from being metabolized. 5α-reductase type I and type II are responsible for approximately one-third and two-thirds of systemic DHT production, respectively.

1. Benign prostatic hyperplasia (BPH), also called benign enlargement of the prostate (BEP), adenofibromyomatous hyperplasia is an increase in size of the prostate.

BPH involves hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate. When sufficiently large, the nodules compress the urethral canal to cause partial, or sometimes virtually complete, obstruction of the urethra, which interferes with the normal flow of urine. It leads to symptoms of urinary hesitancy, frequent urination, dysuria (painful urination), increased risk of urinary tract infections, and urinary retention. Although prostate specific antigen levels may be elevated in these patients because of increased organ volume and inflammation due to urinary tract infections, BPH does not lead to cancer or increase the risk of cancer.

As per the guideline “Management of Benign prostatic hyperplasia”:-

When deciding on the treatment, cost-effectiveness should also be evaluated (i.e., when would invasive therapy, which usually gives complete cure, cost less and be more convenient for the patient than drug therapy continuing for years). Transurethral resection is more cost-effective than drug treatment. A combination of 5-alpha-reductase inhibitor and alpha1-blocker alleviates symptoms more effectively than either drug alone.

With the 5-Alpha-Reductase Inhibitors treatment (finasteride/ dutasteride), the symptoms are alleviated, the urine flow is increased, and the obstruction is decreased. The effect is at its best in patients with large prostates. The effect starts slowly, sometimes as late as 6 months after the onset of treatment. If no effect is observed in 6 months the indications for surgery should be reconsidered. Although treatment with 5-alpha-reductase inhibitors decreases serum PSA level by about 50% this makes follow-up no more difficult than with alpha-blockers: an increasing PSA concentration is an indication for investigation by an urologist.

2. Androgenic alopecia is hair loss that occurs due to an underlying susceptibility of hair follicles to androgenic miniaturization. It is the most common cause of hair loss and will affect up to 70% of men and 40% of women at some point in their lifetime. Men typically present with hairline recession at the temples and vertex balding while women normally diffusely thin over the top of their scalps. Both genetic and environmental factors play a role, and many etiologies remain unknown.

Finasteride is the most common treatment approach for Androgenic alopecia. It is a synthetic type II 5α reductase inhibitor that reduces the conversion of testosterone to DHT.16 Improvement in hair count and thickness is possible, with responsiveness improving over 6 months to 1 year with 1 mg daily intake. Finasteride has significant, adverse consequences for the development of male embryos and, as such, it is not officially approved for use in women.

2.3 Unknowns relating to treatment benefits

No Unknowns relating to treatment benefits have been identified for finasteride.

2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Breast cancer in men (Breast swelling or tenderness)	Breast cancer has been reported in men taking finasteride during clinical trials and in the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.	Yes, • You should promptly report to your doctor any changes in your breast tissue such as lumps, pain, enlargement or nipple discharge as these may be signs of a serious condition, such as breast cancer.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Exposure in Pregnancy - risk to male foetus	• The ability of 5α-Reductase-inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, might cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman. • Women should not handle crushed or broken tablets of finasteride when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus.

Important missing information

Risk	What is known
Breastfeeding	Contraindicated in women and children.

2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

2.6 Planned post authorisation development plan

Not applicable

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
Not applicable	Not applicable	Not applicable	Not applicable