1 Elements for summary tables in the EPAR

1.1 Summary table of Safety concerns

Summary of safety concerns	
Important Identified risks	Sexual adverse events - altered [decreased] libido, impotence, ejaculation disorders), that may persist after discontinuation of drug Breast disorders (enlargement and tenderness) Cardiac failure Depressed mood <u>Associated with tamsulosin:</u> SJS, dermatitis exfoliative and erythema multiforme Priapism
Important Potential risks	Cardiovascular events (other than cardiac failure) including atrial fibrillation, tachycardia and arrhythmias associated with tamsulosin Male breast cancer High-grade prostate cancer Interference with formation of external male genitalia in the foetus
Missing information	Men with severe hepatic impairment Men with unstable medical conditions such as recent myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident; cancer; or uncontrolled diabetes or peptic ulcer disease.

1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
N/A				

1.3 Summary of post authorisation efficacy development plan

Description of study (including objectives and study number)	Milestone(s)	Due Date(s)
FDC114615 (CONDUCT) A two year, multi-centre, randomised, open-label trial to assess the efficacy of DUODART (dutasteride plus tamsulosin) when compared to the standard practice of watchful waiting, with a defined escalation to tamsulosin in treatment naive men with symptomatic benign prostate hyperplasia (BPH). Primary objective: to assess the efficacy of DUODART treatment plus lifestyle advice in providing superior symptomatic improvement to treatment naïve BPH subjects compared with watchful waiting plus lifestyle advice plus step-up therapy with tamsulosin. Secondary objectives: • BPH Impact Index score • BPH-related Health Status • Clinical progression • BPH-related prostatic surgery • Question 1 - Patient Perception of Study Treatment Questionnaire (PPST) • Question 2 - PPST • Safety and tolerability	Study finish	March 2014

1.4 Summary table of Risk Minimisation Measures

Safety concern 1	**Reproductive systems:** Sexual adverse events of altered [decreased] libido, impotence, ejaculation disorders that may persists after discontinuation of drug Breast disorders (enlargement and tenderness)
Routine risk	SmPC:

minimisation measures:	**Section 4.8 Undesirable effects** Data from the co-administration of dutasteride and tamsulosin from the 4 year analysis of the CombAT (Combination of Avodart and Tamsulosin) study describe impotence, altered libido, ejaculation disorders and breast disorders as common in the SmPC. A footnote has been added inform that i sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is not known. PL includes comparable wording
Additional risk minimisation measure(s):None	None required.
Safety concern 2	**Cardiac failure**
Routine risk minimisation measures	SmPC: **Section 4.4 Special warnings and precautions for use** *Cardiac failure* Data from two 4-year clinical studies, on the incidence of cardiac failure are provided. **Section 4.8 Undesirable Effects** Data from the co-administration of dutasteride and tamsulosin from the 4 year analysis of the CombAT (Combination of Avodart and Tamsulosin) study, describe cardiac failure (composite terms) as uncommon in the SmPC. **Section 5.1 Pharmacodynamic properties** Cardiac failure: Data on cardiac failure from two 4 year studies are provided. Data from meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies are provided. PL includes comparable wording.
Additional risk minimisation measure(s) None	None required
Safety concern 3	**Depressed mood**
Routine risk minimisation measures	SmPC: **Section 4.8 Undesirable effects** Other data from post marketing experience list depression. PL includes comparable wording
Additional risk minimisation measure(s):	None required.

Safety concern 4	**Steven-Johnson Syndrome (SJS) associated with tamsulosin**
Routine risk minimisation measures	N/A
Additional risk minimisation measure(s): None	N/A
Safety concern 5	**Cardiovascular events (other than cardiac failure) including atrial fibrillation, tachycardia and arrhythmias associated with tamsulosin**
Routine risk minimisation measures	N/A
Additional risk minimisation measure(s): None	N/A
Safety concern 6	**Male breast cancer**
Routine risk minimisation measures	SmPC: **Section 4.4 Special warnings and precautions for use** *Breast neoplasia* There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-alpha reductase inhibitors (see section 5.1). Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. **Section 4.8 Undesirable effects** OTHER DATA The following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4). **Section 5.1 Pharmacodynamic properties** Breast neoplasia: Data from 2-year clinical trials, 2 reports of breast cancer were received in dutasteride treated patients. No reports were received during the CombAT and REDUCE studies. Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6,780 controls) and the other in a UK (n=398 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5 ARIs (see section 4.4). Results from the first study did not identify a positive association for male breast cancer (relative risk for 1 year of use before breast cancer diagnosis compared with < 1 year of use: 0.70: 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5-alpha reductase inhibitors compared with non-use was 1.08: 95% CI 0.62, 1.87). A causal relationship between the occurrence of male breast cancer and long term use of dutasteride has not been established. PL includes comparable wording.

Additional risk minimisation measure(s): None	None required.
Safety concern 7	**High-grade prostate cancer**
Routine risk minimisation measures	SmPC: **Section 4.4 Special warnings and precautions for use** *Prostate specific antigen (PSA)* Informs that patients should be evaluated for prostate cancer or other conditions which can cause the same symptoms as BPH, prior to initiating therapy with Duodart and periodically thereafter. Also informs that a new PSA baseline established after 6 months of treatment with Duodart. *Prostate cancer and high grade tumours* Warns that men taking Combodart should be regularly evaluated for prostate cancer risk including PSA testing. **Section 4.8 Undesirable effects** OTHER DATA Informs that in the REDUCE study a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo. **Section 5.1 Pharmacodynamic properties** Dutasteride Prostate cancer and high grade tumours There was a higher incidence of Gleason 8-10 prostate cancers in the Avodart group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%) (p=0.15). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the Avodart group (n=17, 0.5%) and the placebo group (n=18, 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the Avodart group (n=12, 0.5%) compared with the placebo group (n=1, <0.1%) (p=0.0035). There are no data available on the effect of Avodart beyond 4 years in men at risk of prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the Avodart group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively) (see section 4.4). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81). The additional 2-year follow-up study of the REDUCE trial did not identify any new cases of Gleason 8–10 prostate cancers. In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were (n=8, 0.5%) for Avodart, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy. Four different epidemiological, population-based studies (two of which were based on a total population of 174,895, one on a population of 13,892, and one on a population of 38,058) showed that the use of 5-alpha reductase inhibitors is not

	associated with the occurrence of high grade prostate cancer, nor with prostate cancer, or overall mortality. In a long-term follow up study (up to 18 years) of another 5-alpha reductase inhibitor (finasteride) with a similar safety profile to dutasteride, there was no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1.02, 95% CI 0.97-1.08) or survival after prostate cancer diagnoses (HR 1.01, 95% CI 0.85-1.20). The relationship between dutasteride and high grade prostate cancer is not clear. PL includes comparable wording.
Additional risk minimisation measure(s): None	None required
Safety concern 8	**Interference with formation of external male genitalia in the foetus resulting in hypospadias**
Routine risk minimisation measures	SmPC: **Section 4.3 Contraindications** Avodart is contraindicated in: - Women and children and adolescents (see section 4.6). **Section 4.6 Fertility, pregnancy and lactation** Avodart is contraindicated for use by women. There have been no studies to investigate the effect of Avodart on pregnancy, lactation and fertility. Pregnancy Warns that as with other 5 alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Informs that, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom. PL includes comparable wording.
Additional risk minimisation measure(s):	None required.
Safety concern 9	**Priapism associated with tamsulosin**
Routine risk minimisation measures	N/A
Additional risk minimisation measure(s):	N/A

Safety concern 10	Men with severe hepatic impairment
Routine risk minimisation measures	SmPC: **Section 4.2 Posology and method of administration** Hepatic impairment The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of dutasteride is contraindicated. **Section 4.3 Contraindications** Avodart is contraindicated in: - patients with severe hepatic impairment. **Section 4.4 Special warnings and precautions for use** Hepatic impairment Dutasteride was not studied in patients with liver disease. Caution should be used in the administration of dutasteride to patients with mild to moderate hepatic impairment. **Section 5.2 Pharmacokinetic properties** The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied. Because dutasteride is eliminated mainly through metabolism the plasma levels of dutasteride are expected to be elevated in these patients and the half-life of dutasteride be prolonged. PL includes comparable wording.
Additional risk minimisation measure(s):	None required.
Safety concern 11	Men with unstable medical conditions such as recent myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident; cancer; or uncontrolled diabetes or peptic ulcer disease.
Routine risk minimisation measures	Many men have developed unstable medical conditions during long-term clinical trials of dutasteride monotherapy and dutasteride + tamsulosin co-administration. No risk minimisation activities are in place as there is no evidence from controlled clinical trials of additional safety concerns in men taking dutasteride who developed these conditions.
Additional risk minimisation measure(s):	None required.

2 Elements for a Public Summary

2.1 Overview of disease epidemiology

Non-cancerous enlargement of the prostate gland (benign prostatic hyperplasia) is mainly found in men aged 50 years and over. This disease can lead to difficulty in starting to urinate and the need empty the bladder frequently. If left untreated, there is a risk that the patient may stop being able to pass urine altogether (Marks, 2006).

Urinary problems in men become more common as they get older. Around 60 out of 100 men aged 40-59 years, and 80 out of 100 men aged over 60 years, were affected by urinary problems in Europe in 2005 (Irwin, 2006).

The risk of developing an enlarged prostate increases with age and also in men who are overweight, have high blood sugar levels, or diabetes (Marks, 2006; Parsons 2006; Hammarsten, 2001; Freeman, 2011).

2.2 Summary of treatment benefits

Dutasteride belongs to a group of medicines called 5-alpha reductase inhibitors and tamsulosin belongs to a group of medicines called alpha-blockers. Dutasteride + Tamsulosin are a combination of two medicines, dutasteride and tamsulosin hydrochloride:

- Dutasteride lowers the production of a hormone called dihydrotesterone, which helps to shrink the prostate gland and relieve symptoms.
- Tamsulosin hydrochloride relaxes the muscles in the prostate gland, giving quick relief of symptoms.

The effect of dutasteride alone, tamsulosin alone, or a combination of both medicines (dutasteride + tamsulosin) was studied in 4,844 male patients with enlarged prostate glands. After 2 years of treatment, patients taking dutasteride + tamsulosin showed a greater improvement in their symptoms and urine flow, compared with patients taking either dutasteride or tamsulosin alone. Their prostate glands also decreased in size more than those taking tamsulosin alone.

2.3 Unknowns relating to treatment benefits

Dutasteride and Dutasteride + tamsulosin have not been studied in patients with liver or kidney disease or men with unstable medical conditions such as recent myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident; cancer; or uncontrolled diabetes or peptic ulcer disease. Younger patients and women have not been studied since BPH is a disease of older men. Most patients in clinical studies were Caucasian; there is no evidence that dutasteride + tamsulosin would be less effective in people from other races.

2.4 Summary of safety concerns

Important Identified risks

Risk	What is known	Preventability
Sexual disorders - Decreased sex drive, not able to achieve or maintain erection (impotence), or difficulty with ejaculation. Some of these events may continue after stopping drug use. (Sexual adverse events – altered [decreased] libido, impotence, ejaculation disorders that may persist after discontinuation of drug.) Breast disorders – swollen (gynecomastia) or painful breasts	In clinical studies patients taking Dutasteride + Tamsulosin were more likely to develop a decreased sex drive, impotence and difficulty with ejaculation compared with those taking dutasteride alone. The doctor's prouduct information for Dutasteride + Tamsulosin advises that these types of sexual problems may develop and are described as common side effects to Dutasteride + tamsulosin treatment (affecting between 1 in 10 and 1 in 100 people). Some of these events may continue after discontinuing Dutasteride +Tamsulosin. A small number of patients taking Dutasteride + Tamsulosin also experienced enlarged or painful breasts. In the majority of these cases the breast disorder was not serious. Although the patients did not recover during the study, they were not followed up afterwards to see when the breast disorders resolved.	. Most sexual side effects are tranistent and reversible. On treatment cessation these side effects resolve spontaneously. If breast enlargement or tenderness is troublesome or if there is nipple discharge patients should consult the physician. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge
Heart failure (Cardiac failure)	In some clinical studies, more patients taking dutasteride and another medicine called an alpha-blocker like tamsulosin experienced heart failure than patients taking only dutasteride or	The doctor's product information for dutasteride + tamsulosin warns about the risk of heart failure. It is described as an uncommon event (affecting between 1 in 100 and 1 in 1000

Risk	What is known	Preventability
	only an alpha-blocker. Heart failure means your heart does not pump blood as well as it should. It is not known why dutasteride + tamsulosin may increase the risk of heart failure.	people).
Depression (Depressed mood)	A small number of post-marketing reports of depression or depressive symptoms have been received. Some of these reports described depressive symptoms starting within 1 month of starting dutasteride + tamsulosin. Some reports describe recovery from symptoms when dutasteride + tamsulosin were stopped.	The product information leaflet warns about the possible side effect "depression". This side effect occurred in a small number of men, but their exact frequency cannot be estimated from the available data
Serious skin reaction (known as Stevens – Johnson Syndrome, erythema multiforme – a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals; dermatitis exfoliative – a scaly rash involving most of the skin) (SJS, dermatitis exfoliative and erythema multiforme associated with tamsulosin)	As seen in a small number of post-marketing reports, these types of reactions are known to be associated with tamsulosin which is contained in dutasteride + tamsulosin. This is a very rare side effect, which affects less than 1 in 10,000 patients treated with tamsulosin.	Patients with a previous allergic reaction to dutasteride + tamsulosin or any ingredient in the capsule should not receive dutasteride + tamsulosin.
Persistent painful erection of the penis in patients taking tamsulosin (Priapism associated with tamsulosin)	In clinical trials, persistent painful erection (priapism) was very rare reported in less than 1 in 10,000 in patients taking tamsulosin.	The doctor's product information advices that, although very rare, persistent painful erection of the penis may occur with tamsulosin, a medicine in dutasteride + tamsulosin. If this happens, get medical help right away. If priapism is not treated, there could be lasting damage to the penis, including not being able to have an erection.

Risk	What is known (Including reason why it is considered a potential risk)
Disease of the heart (other than heart failure), including abnormal or fast heartbeat in patients taking tamsulosin. (Cardiovascular events (other than cardiac failure), including atrial fibrillation, tachycardia and arrhythmias associated with tamsulosin)	There is a theoretical risk that a reduction in a hormone called DHT, which is caused by dutasteride portion of the dutasteride+tamsulosin capsule, may increase the risk of heart problems. In a clinical study no important differences were seen between patients receiving dutasteride, dutasteride+tamsulosin or just tamsulosin. There have been reports of irregular heartbeats with tamsulosin which is part of the dutasteride+tamsulosin capsule. In clinical trials few patients taking dutasteride and tamsulosin suffered from an irregular heartbeat or a fast heartbeat.
Male breast cancer	There have been a small number of reports from patients who have been prescribed dutasteride and have developed breast cancer. The association of dutasteride with male breast cancer is not clear.
Prostate cancer (High grade prostate cancer)	In a clinical study of men at increased risk of prostate cancer, men taking dutasteride had a serious form of prostate cancer more often than men who did not take dutasteride. The effect of dutasteride on this serious form of prostate cancer is not clear. The doctor's product information advises that patients receiving dutasteride or dutasteride + tamsulosin should be checked for prostate cancer risk after 6 months of treatment, and should be monitored regularly throughout treatment.
Abnormal genital development in unborn male babies (Interference with formation of external male genitalia in the foetus)	A very small amount of dutasteride has been found in the semen of men taking dutasteride + tamsulosin. Dutasteride portion of the dutasteride +tamsulosin capsule can be absorbed through the skin. Dutasteride can affect the normal development of a male baby. This is a particular risk in the first 16 weeks of pregnancy. It is advised that patients use condoms during sexual intercourse to prevent this exposure. No reports have been seen in clinical trials. The doctor's product information advises that Pregnant women should not touch the dutasteride + tamsulosin capsules. If a woman who is pregnant with a male baby gets enough dutasteride in her body by swallowing or touching the capsules, the male baby may be born with sex organs that are not normal. If a pregnant woman or woman of childbearing potential comes in contact with leaking capsules, the contact area should be washed

Risk	What is known (Including reason why it is considered a potential risk)
	immediately with soap and water.

Missing information

Risk	What is known
Severe liver problems (Severe hepatic impairment)	The safety and effectiveness of dutasteride + tamsulosin in patients with severe liver problems has not been studied. Due to the way in which dutasteride is broken down by the body, it is expected that amounts of dutasteride will be higher in patients with severe liver problems, and the effect of the drug will last for a longer period of time than in patients without severe liver problems.
Men with conditions such as recent heart attack, heart bypass surgery, restriction of blood supply to the heart (angina), abnormal or irregular heartbeat, heart failure, stroke, cancer, abnormal blood sugar levels (diabetes) and stomach ulcers."	Patients with these unstable co-existing conditions have not been studied and were excluded from clinical trials.

2.5 Summary of 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.

The Summary of Product Characteristics and the Package leaflet for Combodart/Duodart can be found in the Combodart/Duodart EPAR page.

This medicine has no additional risk minimisation measures.

2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity	*Objective*	*Safety concern/efficacy issue addressed*	*Status*	*Planned date for submission of final results*
FDC114615 (CONDUCT)	To compare dutasteride-tamsulosin treatment plus lifestyle advice to no treatment plus lifestyle advice plus step-up therapy with tamsulosin.	No safety concerns – studied how well dutasteride-tamsulosin works (efficacy)	Complete	4Q2014
FDC116115	A prospective study of sexual function in sexually active men treated for BPH with DUODART. To assess the change in sexual function from baseline to 1 year in sexually active men with at least moderate BPH (international prostate symptom score - IPSS = or > 12) who are treated with DUODART, compared to men treated with placebo.	Sexual adverse reactions	Complete	March 2017
200209	A prospective study of sexual function in men taking dutasteride for the treatment of androgenetic alopecia. To evaluate adverse events (AEs) related to sexual function	Sexual adverse reactions	Complete	4Q2016
WEUSKOP5723 5ARI prostate mortality study	To assess the risk of prostate cancer mortality associated	Prostate cancer	Complete	3Q2016

	with use of 5ARIs compared to alpha-blockers in men treated with BPH medications.			

Studies which are a condition of the marketing authorisation

No dutasteride and dutasteride-tamsulosin studies were a condition of the marketing authorisation.

2.7 Summary of changes to the Risk Management Plan over time

Table 35 Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comment
3	25 Apr 2011	Included Year 4 data from Study ARI40005, as well as relevant safety data from dutasteride monotherapy trials in men with BPH and in men at increased risk of prostate cancer and was aligned with v03 of the EU RMP for dutasteride-tamsulosin.	
4	18 November 2011, Version 4)	Included the results of the FDA analysis of prostate volume and detection bias. The absolute risk increase of high-grade prostate cancer for dutasteride compared to placebo and finasteride compared to placebo was added. Amending text throughout the RMP change “cardiac failure” from a potential risk to identified.	
5	19/May/2012	Depressed mood was	Information on

Version	Date	Safety Concerns	Comment
		added as Identified Risk	depressed mood were added to the safety specification.
6	19/November/2012	Updates to the sexual adverse reaction risk sections.	Information on sexual side effects was updated to add clarification wording regarding sexual adverse events (altered [decreased] libido, impotence, ejaculation disorders) that these events may persist after drug discontinuation.
7	20May2013	Version 7 is the first RMP in the new EU_RMP template	No new risks were added to this plan. No new safety data other than these data required by the template.