Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combodart 0.5 mg/0.4 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride, (equivalent to 0.367 mg tamsulosin).

Contains Sunset Yellow (E 110). Each capsule contains ≤ 0.1 mg sunset yellow.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Product imported from Poland:
Oblong, hard capsules with a brown body and an orange cap imprinted with GS 7CZ in black ink. Each hard capsule contains tamsulosin hydrochloride modified release pellets and one dutasteride soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

For information on effects of treatment and patient populations studied in clinical trials please see section 5.1.

4.2 Posology and method of administration

Adults (including elderly):
The recommended dose of Combodart is one capsule (0.5 mg/ 0.4 mg) taken orally approximately 30 minutes after the same meal each day. The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Where appropriate, Combodart may be used to substitute concomitant dutasteride and tamsulosin hydrochloride in existing dual therapy to simplify treatment.

Where clinically appropriate, direct change from dutasteride or tamsulosin hydrochloride monotherapy to Combodart may be considered.

Renal impairment
The effect of renal impairment on dutasteride-tamsulosin pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment (see section 4.4 and 5.2).

Hepatic impairment
The effect of hepatic impairment on dutasteride-tamsulosin pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment (see section 4.4 and section 5.2). In patients with severe hepatic impairment, the use of Combodart is contraindicated (see section 4.3).

4.3 Contraindications

Combodart is contraindicated in:

- women and children and adolescents (see section 4.6).
- patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin (including tamsulosin-induced angio-edema), soya, peanut or any of the other excipients.
- patients with a history of orthostatic hypotension.
- patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events (including cardiac failure) and after consideration of alternative treatment options including monotherapies.

Cardiac failure
In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies (see section 5.1).

Effects on prostate specific antigen (PSA) and prostate cancer detection
Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with Combodart and periodically thereafter.

Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Combodart causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment..

Patients receiving Combodart should have a new PSA baseline established after 6 months of treatment with Combodart. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on Combodart may signal the presence of prostate cancer (particularly high grade cancer) or noncompliance to therapy with Combodart and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α−reductase inhibitor (see section 5.1). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with Combodart does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established (see section 5.1).

Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of Combodart. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Combodart therapy, no adjustment to its value appears necessary.

Prostate cancer and high grade tumours
Results of one clinical study (the REDUCE study) in men at increase risk of prostate cancer revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men compared to placebo. The relationship between dutasteride and high grade prostate cancer is not clear. Men taking Combodart should be regularly evaluated for prostate cancer risk including PSA testing (see section 5.1).

Renal impairment
The treatment of severely renally impaired patients (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Orthostatic hypotension
As with other alpha-blockers, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with Combodart should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved.

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may lead to increased procedural complications during the operation. The initiation of therapy with Combodart in patients for whom cataract surgery is scheduled is therefore not recommended.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with Combodart in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established.

Leaking capsules
Combodart is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules (see section 4.6). If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

Hepatic impairment
Combodart has not been studied in patients with liver disease. Caution should be used in the administration of Combodart to patients with mild to moderate hepatic impairment (see section 4.2, section 4.3 and section 5.2).

Excipients
This medicinal product contains the colouring agent Sunset Yellow (E110), which may cause allergic reactions.

Breast neoplasia
Breast cancer has been reported in men taking dutasteride in clinical trials (see section 5.1) and during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no drug interaction studies for Combodart. The following statements reflect the information available on the individual components.

Dutasteride

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection, please see section 4.4.

Effects of other drugs on the pharmacokinetics of dutasteride

Use together with CYP3A4 and/or P-glycoprotein-inhibitors:

Dutasteride is mainly eliminated via metabolism. *In vitro* studies indicate that this metabolism is catalysed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1.6 to 1.8 times greater, respectively, in a small number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P-glycoprotein) than in other patients.

Long-term combination of dutasteride with drugs that are potent inhibitors of the enzyme CYP3A4 (e.g. ritonavir, indinavir, nefazodone, itraconazole, ketoconazole administered orally) may increase serum concentrations of dutasteride. Further inhibition of 5-alpha reductase at increased dutasteride exposure, is not likely. However, a reduction of the dutasteride dosing frequency can be considered if side effects are noted. It should be noted that in the case of enzyme inhibition, the long half-life may be further prolonged and it can take more than 6 months of concurrent therapy before a new steady state is reached.

Administration of 12 g cholestyramine one hour after a 5 mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other drugs

In a small study (N=24) of two weeks duration in healthy men, dutasteride (0.5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamic interaction in this study.

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P-glycoprotein. *In vitro* interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

Tamsulosin

Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents and other alpha-1 adrenergic blockers could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha-1 adrenergic blockers.

Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine.

A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited in vitro and in vivo studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant furosemide brings about a fall in plasma levels of tamsulosin, but as levels remain within the normal range posology need not be adjusted.

In vitro neither diazepam nor propranolol, trichlormethiazide, chlormadinon, amitryptyline, diclofenac, glibenclamide and simvastatin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide, and chlormadinon.

No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolising enzyme system), involving amitriptyline, salbutamol and glibenclamide. Diclofenac however, may increase the elimination rate of tamsulosin.

4.6 Fertility, pregnancy and lactation

Combodart is contraindicated for use by women. There have been no studies to investigate the effect of Combodart on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components (see section 5.3).

Fertility

Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men (see section 5.1). The possibility of reduced male fertility cannot be excluded. Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Pregnancy

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 (see section 4.4). Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. It is not known whether a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy).

As with all 5 alpha reductase inhibitors, 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.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits showed no evidence of foetal harm.

For information on preclinical data, see section 5.3.

Lactation

It is not known whether dutasteride or tamsulosin are excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects of Combodart on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Combodart.

4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Combodart; however bioequivalence of Combodart with co-administered dutasteride and tamsulosin has been demonstrated (see section 5.2). The data presented here relate to the co-administration of dutasteride and tamsulosin from the 4 year analysis of the CombAT (Combination of Avodart and Tamsulosin) study, a comparison of dutasteride 0.5mg and tamsulosin 0.4mg once daily for four years as co-administration or as monotherapy. Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided.

DUTASTERIDE AND TAMSULOSIN CO-ADMINISTRATION

Clinical Trial Data

Data from the 4 year CombAT study have shown that the incidence of any investigator-judged drug-related adverse event during the first, second, third and fourth years of treatment respectively was 22% 6%, 4% and 2% for dutasteride + tamsulosin co-administration therapy, 15%, 6%, 3% and 2% for dutasteride monotherapy and 13%, 5%, 2% and 2% for tamsulosin monotherapy. The higher incidence of adverse events in the co-administration therapy group in the first year of treatment was due to a higher incidence of reproductive disorders, specifically ejaculation disorders, observed in this group.

The following investigator-judged drug-related adverse events have been reported with an incidence of greater than or equal to 1% during the first year of treatment in the CombAT Study; the incidence of these events during the four years of treatment is shown in the table below:

System Organ Class	Adverse Reaction	Incidence during treatment period			
		Year 1	Year 2	Year 3	Year 4
	Combination[a] (n)	(n=1610)	(n=1428)	(n=1283)	(n=1200)
	Dutasteride	(n=1623)	(n=1464)	(n=1325)	(n=1200)
	Tamsulosin	(n=1611)	(n=1468)	(n=1281)	(n=1112)
Nervous system disorders	Dizziness				
	Combination[a]	1.4%	0.1%	<0.1%	0.2%
	Dutasteride	0.7%	0.1%	<0.1%	<0.1%
	Tamsulosin	1.3%	0.4%	<0.1%	0%
Cardiac disorders	Cardiac failure (composite term[b])				
	Combination[a]	0.2%	0.4%	0.2%	0.2%
	Dutasteride	<0.1%	0.1%	<0.1%	0%
	Tamsulosin	0.1%	<0.1%	0.4%	0.2%
Reproductive system and breast disorders, Psychiatric disorders, Investigations	Impotence				
	Combination[a]	6.3%	1.8%	0.9%	0.4%
	Dutasteride	5.1%	1.6%	0.6%	0.3%
	Tamsulosin	3.3%	1.0%	0.6%	1.1%
	Altered (decreased) libido				
	Combination[a]	5.3%	0.8%	0.2%	0%
	Dutasteride	3.8%	1.0%	0.2%	0%
	Tamsulosin	2.5%	0.7%	0.2%	<0.1%
	Ejaculation disorders				
	Combination[a]	9.0%	1.0%	0.5%	<0.1%
	Dutasteride	1.5%	0.5%	0.2%	0.3%
	Tamsulosin	2.7%	0.5%	0.2%	0.3%
	Breast disorders[c]				
	Combination[a]	2.1%	0.8%	0.9%	0.6%
	Dutasteride	1.7%	1.2%	0.5%	0.7%
	Tamsulosin	0.8%	0.4%	0.2%	0%
Nervous system disorders					

[a] Combination = dutasteride 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

[b] Cardiac failure composite term comprised of Cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.

[c] Includes breast tenderness and breast enlargement.

DUTASTERIDE MONOTHERAPY

Clinical Trial Data
In three phase III placebo-controlled studies of Dutasteride treatment (n =2167) compared to placebo (n=2158), investigator−judged drug−related adverse events after one and two years of therapy were similar in type and frequency to those observed in the dutasteride monotherapy arm of the CombAT study (see table above).
No change in the adverse event profile was apparent over a further 2 years in an open−label extension phase of these studies.

Post marketing Data
Adverse events from post-marketing experience are identified from spontaneous post-marketing reports; therefore the true incidence is unknown.

Immune system disorders
Unknown: Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.

Skin and subcutaneous tissue disorders
Uncommon: Alopecia (primarily body hair loss), hypertrichosis.

TAMSULOSIN MONOTHERAPY

Clinical Trial Data and Postmarketing Data
The adverse reactions and frequency categories listed in the table below are based on information available in the public domain. Common and uncommon reactions are consistent with those identified in a clinical trial setting and the frequency categories generally reflect incidence over placebo. Rare and very rare reactions are consistent with those identified from post marketing reports and the frequency categories reflect reporting rates.

	Frequency Category			
System Organ Class	Common (≥1/100 <1/10)	Uncommon (≥1/1000 <1/100)	Rare (≥1/10,000 <1/1000)	Very rare (<1/10,000) including isolated cases
Nervous system disorders	Dizziness	Headache	Syncope	
Cardiac disorders		Palpitations		
Vascular disorders		Postural hypotension		
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal disorders		Constipation Diarrhoea Nausea Vomiting		
Skin and subcutaneous disorders		Rash, Pruritis, Urticaria	Angioedema	
Reproductive system and breast disorders		Abnormal ejaculation		Priapism
General disorders and administration site disorders		Asthenia		

During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha-1 blocker therapy, including tamsulosin (see section 4.4).

OTHER DATA

The REDUCE study revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo (see sections 4.4 and 5.1). Whether the effect of dutasteride to reduce prostate volume, or study related factors, impacted the results of this study has not been established.

The following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4).

4.9 Overdose

No data are available with regard to overdosage of Combodart. The following statements reflect the information available on the individual components.

Dutasteride

In volunteer studies, single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg. There is no specific antidote for dutasteride, therefore, in suspected overdosage symptomatic and supportive treatment should be given as appropriate.

Tamsulosin

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed which were treated with fluid replacement and the patient could be discharged the same day. In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders, and when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52

Dutasteride-tamsulosin is a combination of two drugs: dutasteride, a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α_{1a} and α_{1d} adrenoreceptors. These drugs have complementary mechanisms of action that rapidly improve symptoms, urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

Dutasteride inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for prostate growth and BPH development. Tamsulosin inhibits α_{1a} and α_{1d} adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α_1-receptors in the prostate are of the α_{1a} subtype.

DUTASTERIDE CO-ADMINISTRATION WITH TAMSULOSIN

There have been no clinical studies conducted with Combodart. The following statements reflect the information available on dutasteride and tamsulosin co-administration therapy.

Dutasteride 0.5 mg/day (n = 1,623), tamsulosin 0.4 mg/day (n = 1,611) or the co-administration of Dutasteride 0.5 mg plus tamsulosin 0.4 mg (n = 1,610) were evaluated in male subjects with moderate to severe symptoms of BPH who had prostates ≥30ml and a PSA value within the range 1.5-10 ng/mL in a 4 year multicentre, multinational, randomized double−blind, parallel group study. Approximately 53% of subjects had previous exposure to 5-alpha reductase inhibitor or alpha-blocker treatment. The primary efficacy endpoint during the first 2 years of treatment was change in International Prostate Symptom Score (IPSS), an 8-item instrument based on AUA-SI with an additional question on quality of life. Secondary efficacy endpoints at 2 years included maximum urine flow rate (Qmax) and prostate volume. The combination achieved significance for IPSS from Month 3 compared to dutasteride and from Month 9 compared to tamsulosin. For Qmax combination achieved significance from Month 6 compared to both dutasteride and tamsulosin.

The combination of dutasteride and tamsulosin provides superior improvement in symptoms than either component alone. After 2 years of treatment, co-administration therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units.

These improvements in flow rate and BII were statistically significant for co-administration therapy compared to both monotherapies.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for co-administration therapy compared to tamsulosin monotherapy alone.

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. After 4 years of treatment, combination therapy statistically significantly reduced the risk of AUR or BPH-related surgery (65.8% reduction in risk p<0.001 [95% CI 54.7% to 74.1%]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 11.9% for tamsulosin (p<0.001). Compared to dutasteride monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6% (p=0.18 [95% CI -10.9% to 41.7%]). The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 5.2% for dutasteride.

Secondary efficacy endpoints after 4 years of treatment included time to clinical progression (defined as a composite of: IPSS deterioration by ≥4 points, BPH-related events of AUR, incontinence, urinary tract infection (UTI), and renal insufficiency) change in International Prostate Symptom Score (IPSS), maximum urine flow rate (Qmax) and prostate volume. IPSS is an 8-item instrument based on the AUA-SI with an additional question on quality of life. Results following 4 years of treatment are presented below:

Parameter	Time-point	Combination	Dutasteride	Tamsulosin
AUR or BPH related surgery (%)	Incidence at Month 48	4.2	5.2	11.9a
Clinical progression* (%)	Month 48	12.6	17.8b	21.5a
IPSS (units)	[Baseline] Month 48 (Change from Baseline)	[16.6] -6.3	[16.4] -5.3b	[16.4] -3.8a
Qmax (mL/sec)	[Baseline] Month 48 (Change from Baseline)	[10.9] 2.4	[10.6] 2.0	[10.7] 0.7a
Prostate Volume (ml)	[Baseline] Month 48 (% Change from Baseline)	[54.7] -27.3	[54.6] -28.0	[55.8] +4.6a

Prostate Transition Zone Volume (ml)#	[Baseline] Month 48 (% Change from Baseline)	[27.7] -17.9	[30.3] -26.5	[30.5] 18.2a
BPH Impact Index (BII) (units)	[Baseline] Month 48 (Change from Baseline)	[5.3] -2.2	[5.3] -1.8b	[5.3] -1.2a
IPSS Question 8 (BPH-related Health Status) (units)	[Baseline] Month 48 (Change from Baseline)	[3.6] -1.5	[3.6] -1.3b	[3.6] -1.1a

Baseline values are mean values and changes from baseline are adjusted mean changes.

* Clinical progression was defined as a composite of: IPSS deterioration by ≥4 points, BPH-related events of AUR, incontinence, UTI, and renal insufficiency.

\# Measured at selected sites (13% of randomized patients)

a. Combination achieved significance ($p<0.001$) vs. tamsulosin at Month 48

b. Combination achieved significance ($p<0.001$) vs. dutasteride at Month 48

DUTASTERIDE

Dutasteride 0.5 mg/day or placebo was evaluated in 4325 male subjects with moderate to severe symptoms of BPH who had prostates ≥30ml and a PSA value within the range 1.5 - 10 ng/mL in three primary efficacy 2-year multicenter, multinational, placebo controlled, double-blind studies. The studies then continued with an open-label extension to 4 years with all patients remaining in the study receiving dutasteride at the same 0.5 mg dose. 37% of initially placebo-randomized patients and 40% of dutasteride-randomized patients remained in the study at 4 years. The majority (71%) of the 2,340 subjects in the open-label extensions completed the 2 additional years of open-label treatment.

The most important clinical efficacy parameters were American Urological Association Symptom Index (AUA-SI), maximum urinary flow (Qmax) and the incidence of acute urinary retention and BPH-related surgery.

AUA-SI is a seven-item questionnaire about BPH-related symptoms with a maximum score of 35. At baseline the average score was approx. 17. After six months, one and two years treatment the placebo group had an average improvement of 2.5, 2.5 and 2.3 points respectively while the Avodart group improved 3.2, 3.8 and 4.5 points respectively. The differences between the groups were statistically significant. The improvement in AUA-SI seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Qmax (maximum urine flow):

Mean baseline Qmax for the studies was approx 10 ml/sec (normal Qmax ≥ 15 ml/sec). After one and two years treatment the flow in the placebo group had improved by 0.8 and 0.9 ml/sec respectively and 1.7 and 2.0 ml/sec respectively in the Avodart group. The difference between the groups was statistically significant from Month 1 to Month 24. The increase in maximum urine flow rate seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Acute Urinary Retention and Surgical Intervention

After two years of treatment, the incidence of AUR was 4.2% in the placebo group against 1.8% in the Avodart group (57% risk reduction). This difference is statistically significant and means that 42 patients (95% CI 30-73) need to be treated for two years to avoid one case of AUR.

The incidence of BPH-related surgery after two years was 4.1% in the placebo group and 2.2% in the Avodart group (48% risk reduction). This difference is statistically significant and means that 51 patients (95% CI 33-109) need to be treated for two years to avoid one surgical intervention.

Hair distribution
The effect of dutasteride on hair distribution was not formally studied during the phase III programme, however, 5 alpha-reductase inhibitors could reduce hair loss and may induce hair growth in subjects with male pattern hair loss (male androgenetic alopecia).

Thyroid function:
Thyroid function was evaluated in a one year study in healthy men. Free thyroxine levels were stable on dutasteride treatment but TSH levels were mildly increased (by 0.4 MCIU/mL) compared to placebo at the end of one year's treatment. However, as TSH levels were variable, median TSH ranges (1.4 - 1.9 MCIU/mL) remained within normal limits (0.5 - 5/6 MCIU/mL), free thyroxine levels were stable within the normal range and similar for both placebo and dutasteride treatment, the changes in TSH were not considered clinically significant. In all the clinical studies, there has been no evidence that dutasteride adversely affects thyroid function.

Breast neoplasia:

In the 2 year clinical trials, providing 3374 patient years of exposure to dutasteride, and at the time of registration in the 2 year open label extension, there were 2 cases of breast cancer reported in dutasteride-treated patients and 1 case in a patient who received placebo. In the 4 year CombAT and REDUCE clinical trials providing 17489 patient years exposure to dutasteride and 5027 patient years exposure to dutasteride and tamsulosin combination, there were no cases of breast cancer reported in any treatment groups.

Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

Effects on male fertility

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in healthy volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all parameters at all time points remained within the normal ranges and did not meet the predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24 week follow-up. The possibility of reduced male fertility cannot be excluded.

Cardiac failure:

In a 4 year BPH study of dutasteride in combination with tamsulosin in 4844 men (the CombAT study) the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: dutasteride, (4/1623, 0.2%) and tamsulosin, (10/1611, 0.6%).

In a separate 4-year study in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL in the case of men 50 to 60 years of age, or 3 ng/mL and 10.0 ng/mL in the case of men older than 60 years of age) (the REDUCE study), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride 0.5 mg once daily (30/4105, 0.7%) compared to subjects taking placebo (16/4126, 0.4%). A post-hoc analysis of this study showed a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects taking dutasteride and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), or placebo and no alpha blocker (15/2727, 0.6%).

Prostate cancer and high grade tumours

In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL in the case of men 50 to 60 years of age, or 3 ng/mL and 10.0 ng/mL in the case of men older than 60 years of age) (the REDUCE study), 6,706 subjects had prostate needle biopsy (primarily protocol mandated) data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6, 70%).

There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride 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 dutasteride 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 dutasteride 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 dutasteride 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 dutasteride 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).

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 dutasteride, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy.

The relationship between dutasteride and high grade prostate cancer is not clear.

TAMSULOSIN

Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in the prostate and urethra, thereby improving voiding symptoms. It also improves the storage symptoms in which bladder instability plays an important role. These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterization is significantly delayed.

A1-adrenoreceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

5.2 Pharmacokinetic properties

Bioequivalence was demonstrated between dutasteride-tamsulosin and concomitant dosing with separate dutasteride and tamsulosin capsules.

The single dose bioequivalence study was performed in both the fasted and fed states. A 30% reduction in Cmax was observed for the tamsulosin component of dutasteride-tamsulosin in the fed state compared to the fasted state. Food had no effect on AUC of tamsulosin.

Absorption

Dutasteride
Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%. The bioavailability of dutasteride is not affected by food.

Tamsulosin
Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Both the rate and extent of absorption of tamsulosin are reduced when taken within 30 minutes of a meal. Uniformity of absorption can be promoted by the patient always taking Combodart after the same meal. Tamsulosin shows dose proportional plasma exposure.

After a single dose of tamsulosin in the fed state, plasma concentrations of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, the mean steady state Cmax in patients is about two thirds higher than that reached after a single dose. Although this was observed in elderly patients, the same finding would also be expected in younger patients.

Distribution

Dutasteride
Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>99.5%). Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months.
Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Tamsulosin
In man tamsulosin is about 99% bound to plasma proteins. The volume of distribution is small (about 0.2l/kg).

Metabolism

Dutasteride
Dutasteride is extensively metabolized *in vivo*. *In vitro*, dutasteride is metabolized by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite.

Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged dutasteride in the faeces.

The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each). Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine.

Tamsulosin
There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Elimination

Dutasteride
The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable.
At low serum concentrations (less than 3 ng/mL), dutasteride is cleared rapidly by both the concentration dependent and concentration independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days.

At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

Tamsulosin
Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged active substance.

Following intravenous or oral administration of an immediate-release formulation, the elimination half life of tamsulosin in plasma ranges from 5 to 7 hours. Due to the absorption rate-controlled pharmacokinetics with tamsulosin modified release capsules, the apparent elimination half life of tamsulosin in the fed state is approximately 10 hours and in the steady state is approximately 13 hours.

Elderly

Dutasteride
Dutasteride pharmacokinetics were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. No significant influence of age was seen on the exposure of dutasteride but the half-life was shorter in men under 50 years of age. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old.

Tamsulosin
Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in elderly males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal impairment

Dutasteride
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no clinically significant increase of the dutasteride plasma concentrations is anticipated for patients with renal impairment (see section 4.2).

Tamsulosin
The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CL_{cr} < 70$ mL/min/1.73m^2) or moderate-severe ($10 \leq CL_{cr} < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects ($CL_{cr} > 90$ mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with endstage renal disease ($CL_{cr} < 10$ mL/min/1.73m^2) have not been studied.

Hepatic impairment

Dutasteride
The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3). 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 (see section 4.2 and section 4.4).

Tamsulosin
The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with Combodart. Dutasteride and tamsulosin hydrochloride individually have been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5 alpha−reductase inhibitors and alpha-adrenergic blockers. The following statements reflect the information available on the individual components.

Dutasteride

Current studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans.

Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride). The clinical relevance of these findings is unknown.

As with other 5 alpha reductase inhibitors, feminisation of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminisation of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

Tamsulosin

Studies of general toxicity and genotoxicity did not show any particular risk to humans other than those related to the pharmacological properties of tamsulosin.

In carcinogenicity studies in rats and mice, tamsulosin hydrochloride produced an increased incidence of proliferative changes of the mammary glands in females.

These findings, which are probably mediated by hyperprolactinaemia and only occurred at high dose levels, are regarded as not clinically relevant

High doses of tamsulosin hydrochloride resulted in a reversible reduction in fertility in male rats considered possibly due to changes of semen content or impairment of ejaculation. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of foetal harm.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Capsule Shell:
Hypromellose
Carrageenan (E407)
Potassium Chloride
Titanium Dioxide (E171)
Iron Oxide Red (E172)
Sunset Yellow (E110)
Carnauba Wax
Maize Starch

Soft Capsule:
Mono-di-glycerides of caprylic/capric acid
Butylhydroxytoluene (E321)

Soft Capsule Shell:
Gelatin
Glycerol
Titanium dioxide (E171)
Iron Oxide Yellow (E172)
Triglycerides, medium chain
Lecithin

Tamsulosin Pellets:
Cellulose, Microcrystalline
Methacrylic acid - ethyl acrylate copolymer 1:1 dispersion 30 per cent (also contains polysorbate 80 and sodium laurilsulfate)
Talc
Triethyl citrate

Black Inks (SW-9010 or SW-9008):
Shellac
Propylene Glycol
Iron Oxide Black (E172)
Potassium Hydroxide (in Black Ink SW-9008 only)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the bottle and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

30 hard capsules in 100 ml bottle, contained in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Dutasteride is absorbed through the skin therefore contact with leaking capsules must be avoided. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water (see section 4.4).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/293/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th November 2012

10 DATE OF REVISION OF THE TEXT