AVODART

1. NAME OF THE MEDICINAL PRODUCT

Avodart 0.5 mg soft capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg dutasteride.

Excipient with known effect
Each capsule contains lecithin (which may contain soya oil). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft.

The capsules are opaque, yellow, oblong soft gelatin capsules marked with GX CE2.

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

Avodart can be administered alone or in combination with the alpha-blocker tamsulosin (0.4mg) (see sections 4.4, 4.8 and 5.1).

Adults (including elderly)

The recommended dose of Avodart is one capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole and not chewed or opened as contact with the capsule contents may result in irritation of the oropharyngeal mucosa. The capsules may be taken with or without food. Although an improvement may be observed at an early stage, it can take up to 6 months before a response to the treatment can be achieved. No dose adjustment is necessary in the elderly.

Renal impairment

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

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 (see section 4.4 and section 5.2). In patients with severe hepatic impairment, the use of dutasteride is contraindicated (see section 4.3).

4.3 Contraindications

Avodart is contraindicated in:
- women and children and adolescents (see section 4.6).
- patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, soya, peanut or any of the other excipients listed in section 6.1.
- 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 (see section 4.2).

Prostate cancer and high grade tumours

The REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled study investigated the effect of dutasteride 0.5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2.5 to 10 ng/ml and a negative prostate biopsy 6 months before study enrolment) compared to placebo. Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (n=29, 0.9%) compared to placebo (n=19, 0.6%). The relationship between dutasteride and Gleason 8 - 10 prostate cancers is not clear. Thus, men taking Avodart should be regularly evaluated for prostate cancer (see section 5.1).

Prostate specific antigen (PSA)

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

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

Treatment with Avodart 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.

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 Avodart. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Avodart therapy, no adjustment to its value appears necessary.

Digital rectal examination, as well as other evaluations for prostate cancer, must be performed on patients prior to initiating therapy with Avodart and periodically thereafter.

Cardiovascular adverse events

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 marginally higher among subjects taking the combination of Avodart and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. However, the incidence of cardiac failure in these trials was lower in all actively treated groups compared to the placebo group, and other data available for dutasteride or alpha-blockers do not support a conclusion on increased cardiovascular risks (see section 5.1).

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.

Leaking capsules

Dutasteride 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

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 (see section 4.2, section 4.3 and section 5.2).

Mood alterations and depression

Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with another oral 5-alpha reductase inhibitor. Patients should be advised to seek medical advice if any of these symptoms occur.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

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.

4.6 Fertility, pregnancy and lactation

Avodart is contraindicated for use by women.

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 Avodart 0.5 mg day. It is not known whether a male foetus may 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.

For information on preclinical data, see section 5.3.

Breast-feeding

It is not known whether dutasteride is excreted in human milk.

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.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties of dutasteride, treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

4.8 Undesirable effects

AVODART AS MONOTHERAPY

Approximately 19% of the 2167 patients who received dutasteride in the 2 year Phase III placebo-controlled trials developed adverse reactions during the first year of treatment. The majority of events were mild to moderate and occurred in the reproductive system. No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

The following table shows adverse reactions from controlled clinical trials and post-marketing experience. The listed adverse events from clinical trials are investigator-judged drug-related events (with incidence more than or equal to 1%) reported with a higher incidence in patients treated with dutasteride compared with placebo during the first year of treatment. Adverse events from post-marketing experience were identified from spontaneous post-marketing reports; therefore the true incidence is not known:

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥1/10,000, < 1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the available data).

Organ system	**Adverse reaction**	**Incidence from clinical trial data**	
		Incidence during year 1 of treatment (n=2167)	**Incidence during year 2 of treatment (n=1744)**
Reproductive system and breast disorders	Impotence*	6.0%	1.7%
	Altered (decreased) libido*	3.7%	0.6%
	Ejaculation disorders*^	1.8%	0.5%
	Breast disorders+	1.3%	1.3%
Immune system disorders	Allergic reactions including rash, pruritus, urticaria, localised oedema, and angioedema	**Incidence estimated from post-marketing data**	
		Not known	
Psychiatric disorders	Depression	Not known	
Skin and subcutaneous tissue disorders	Alopecia (primarily body hair loss), hypertrichosis	Uncommon	
Reproductive system and breast disorders	Testicular pain and swelling	Not known	

* These 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 unknown.

^ includes semen volume decreased

+ includes breast tenderness and breast enlargement

AVODART IN COMBINATION WITH THE ALPHA-BLOCKER TAMSULOSIN

Data from the 4 year CombAT Study, comparing dutasteride 0.5mg (n=1623) and tamsulosin 0.4mg (n=1611) once daily alone and in combination (n=1610) 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 combination 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 combination 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	Impotence [c]				
	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 [c]				
	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 [c^]				
	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[d]				
	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%

[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] These 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 unknown.

[d] Includes breast tenderness and breast enlargement.

[^] Includes semen volume decreased.

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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

In volunteer studies of Avodart, 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 Avodart, therefore, in suspected overdosage symptomatic and supportive treatment should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors, ATC code: G04C B02.

Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5α-reductase isoenzymes which are responsible for the conversion of testosterone to DHT.

AVODART AS MONOTHERAPY

Effects on DHT/Testosterone:

Effect of daily doses of Avodart on the reduction on DHT is dose dependant and is observed within 1-2 weeks (85% and 90% reduction, respectively).
In patients with BPH treated with dutasteride 0.5 mg/day, the median decrease in serum DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years.

Effect on Prostate Volume:

Significant reductions in prostate volume have been detected as early as one month after initiation of treatment and reductions continued through Month 24 ($p<0.001$). Avodart led to a mean reduction of total prostate volume of 23.6% (from 54.9ml at baseline to 42.1ml) at Month 12 compared with a mean reduction of 0.5% (from 54.0ml to 53.7ml) in the placebo group. Significant ($p<0.001$) reductions also occurred in prostate transitional zone volume as early as one month continuing through Month 24, with a mean reduction in prostate transitional zone volume of 17.8% (from 26.8ml at baseline to 21.4ml) in the Avodart group compared to a mean increase of 7.9% (from 26.8ml to 27.5ml) in the placebo group at Month 12. The reduction of the prostate volume seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies. Reduction of the size of the prostate leads to improvement of symptoms and a decreased risk for AUR and BPH-related surgery.

Clinical efficacy and safety

Avodart 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 urinary 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 male 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.

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-alpha reductase inhibitors (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.

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.

AVODART IN COMBINATION WITH THE ALPHA-BLOCKER TAMSULOSIN

Avodart 0.5 mg/day (n = 1,623), tamsulosin 0.4 mg/day (n = 1,611) or the combination of Avodart 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 multicentre, multinational, randomized double-blind, parallel group study (the CombAT 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 Avodart and from Month 9 compared to tamsulosin. For Qmax combination achieved significance from Month 6 compared to both Avodart and tamsulosin.

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 Avodart 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 Avodart.

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. Results following 4 years of treatment are presented below:

Parameter	Time-point	Combination	Avodart	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. Avodart at Month 48

CARDIOVASCULAR ADVERSE EVENTS

In a 4 year BPH study of Avodart 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: Avodart, (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 Avodart 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 Avodart and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects taking Avodart 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%). (see section 4.4).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of Avodart (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

PROSTATE CANCER AND HIGH GRADE TUMOURS
In a 4-year comparison of placebo and Avodart 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 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.

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

Effects on sexual function:

The effects of dutasteride-tamsulosin fixed dose combination on sexual function were assessed in a double-blind, placebo-controlled study in sexually active men with BPH (n=243 dutasteride-tamsulosin combination, n=246 placebo). A statistically significant (p<0.001) greater reduction (worsening) in the Men's Sexual Health Questionnaire (MSHQ) score was observed at 12 months in the combination group. The reduction was mainly related to a worsening of the ejaculation and overall satisfaction domains rather than the erection domains. These effects did not affect study participants' perception of the combination, which was rated with a statistically significant greater satisfaction throughout the duration of the study compared with placebo (p<0.05). In this study the sexual adverse events occurred during the 12 months of treatment and approximately half of these resolved within 6 months post-treatment.

Dutasteride-tamsulosin combination and dutasteride monotherapy are known to cause sexual function adverse effects (see section 4.8).

As observed in other clinical studies, including CombAT and REDUCE, the incidence of adverse events related to sexual function decreases over time with continued therapy.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

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%.

Biotransformation

Dutasteride is extensively metabolised *in vivo*. *In vitro*, dutasteride is metabolised 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.

Elimination

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.

Elderly

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.

Renal impairment

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).

Hepatic impairment

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).

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
mono and diglycerides of caprylic/capric acid (MDC)
butylhydroxytoluene (E321).

Capsule shell:
gelatin
glycerol
titanium dioxide (E171)
iron oxide yellow (E172)
triglycerides, medium chain (MCT)
lecithin (may contain soya oil).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blisters of opaque PVC/PVDC/Aluminium film containing 10 soft gelatin capsules packed into containers of 10, 30, 50, 60 and 90 capsules. Not all pack sizes may be marketed.

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

7. MANUFACTURER

GlaxoSmithKline Trading Services Limited, Dublin, Ireland

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

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