AVODART SOFT CAPSULES 0.5 MG

1. NAME OF THE MEDICINAL PRODUCT

AVODART 0.5 mg capsules, soft.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg dutasteride. For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

AVODART is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce prostate size, reduce the risk of acute urinary retention, and reduce the need for BPH-related surgery.

In addition, *AVODART* in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

4.2. Posology and Method of Administration

Adult males (including elderly):

AVODART can be administered alone or in combination with the alpha-blocker tamsulosin (0.4 mg).

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.

AVODART 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 5.2 Pharmacokinetic Properties).

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 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties). In patients with severe hepatic impairment, the use of dutasteride is contraindicated (See section 4.3 Contraindications).

4.3. Contraindications

AVODART is contraindicated for use in women, children and adolescents (see 4.6 Pregnancy and Lactation).

AVODART is contraindicated in patients with hypersensitivity to dutasteride, other 5-alpha- reductase inhibitors, or any of the excipients.

AVODART is contraindicated in patients with severe hepatic impairment.

4.4. Special Warnings and Special Precautions for Use

Prostate cancer

In a 4-year study of over 8,000 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 (the REDUCE study), 1,517 men were diagnosed with prostate cancer. 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%). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between *AVODART* and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking *AVODART* should be regularly evaluated for prostate cancer risk including PSA testing.

In an additional 2-year follow-up study with the original patients from the dutasteride chemoprevention study (REDUCE), a low rate of new prostate cancers were diagnosed (dutasteride [n=14, 1.2%] and placebo [n=7, 0.7%]), with no new identified cases of Gleason 8–10 prostate cancers.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed 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).

Whether the effect of 5-ARIs to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. The relationship between *AVODART* and high grade prostate cancer is not clear.

Prostate specific antigen (PSA)

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. Generally, a total serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy.

Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking *AVODART* does not exclude a diagnosis of prostate cancer. *AVODART* causes a decrease in serum PSA levels by approximately 50%, after 6 months, in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL).

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 non-compliance 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-ARI. 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, should 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 higher among subjects taking the combination of *AVODART* 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. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between *AVODART* (alone or in combination with an alpha blocker) and cardiac failure has been established (see Clinical Studies).

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.

Breast cancer

There have been rare reports of male breast cancer reported in men taking *AVODART* 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-ARIs (see Clinical Studies). Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

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

Leaking capsules

Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules (see Pregnancy and Lactation). If contact is made with leaking capsules the contact area should be washed immediately with soap and water.

Hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease (see Posology and Method of Administration and Pharmacokinetic Properties).

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 before 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, no pharmacokinetic or pharmacodynamic interaction was observed between dutasteride and tamsulosin or terazosin.

There was no evidence of an interaction when dutasteride was co-administered with tamsulosin in a clinical trial of 327 patients for up to 9 months.

4.6. Pregnancy and Lactation

AVODART is contraindicated for use by women.

Fertility

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal 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 semen parameters at all time points remained within the normal ranges and did not meet 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.

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 4.4 Special Warnings and Special Precautions for Use). Small amounts of dutasteride have been recovered from the semen in subjects receiving *AVODART* 0.5 mg day. Based on studies in animals, it is unlikely that a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with *AVODART* (the risk of which is greatest during the first 16 weeks of pregnancy). However, 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.

Lactation

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

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

Clinical Trial Data

AVODART Monotherapy

Approximately 19% of the 2167 patients who received dutasteride in the Phase III placebo-controlled trials developed adverse reactions. The majority of events were mild to moderate and occurred in the reproductive system.

The following adverse reactions have been reported with a higher incidence than in the placebo groups during the first year of treatment in controlled clinical trials:

Organ system	**Adverse reaction**	**Incidence**
Reproductive system and breast disorders	Impotence*	6.0%
	Altered (decreased) libido*	3.7%
	Ejaculation disorders*	1.8%
	Breast disorders+	1.3%

* 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 breast enlargement and/or breast tenderness

The incidence of adverse events is decreasing with time.
The incidence of more rare adverse reactions or adverse reactions that may occur after long term treatment is currently unknown.

No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

AVODART in combination with the alpha-blocker tamsulosin

The following investigator-judged drug-related adverse events (with a cumulative incidence of greater than or equal to 1%) have been reported in the CombAT (Combination of *AVODART* and Tamsulosin) Study, a comparison of *AVODART* 0.5 mg and tamsulosin 0.4 mg once daily for four years in combination or as monotherapy.

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)
Impotence[b]				
Combination[a]	6%	2%	<1%	<1%
Dutasteride	5%	2%	<1%	<1%
Tamsulosin	3%	1%	<1%	1%
Altered (decreased) libido[b]				
Combination[a]	5%	<1%	<1%	0%
Dutasteride	4%	1%	<1%	0%
Tamsulosin	2%	<1%	<1%	<1%
Ejaculation disorders[b]				
Combination[a]	9%	1%	<1%	<1%
Dutasteride	1%	<1%	<1%	<1%
Tamsulosin	3%	<1%	<1%	<1%
Breast disorders[c]				
Combination[a]	2%	<1%	<1%	<1%
Dutasteride	2%	1%	<1%	<1%
Tamsulosin	<1%	<1%	<1%	0%
Dizziness				
Combination[a]	1%	<1%	<1%	<1%
Dutasteride	<1%	<1%	<1%	<1%
Tamsulosin	1%	<1%	<1%	0%

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

b. 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.

c. Includes breast tenderness and breast enlargement.

Post-marketing Data

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000)

including isolated reports. Frequency categories determined from post-marketing data refer to reporting rate rather than true frequency.

Immune system disorders

Very rare: Allergic reaction, including rash, pruritus, urticaria, localised oedema, and angioedema

Psychiatric disorders

Very rare: Depressed mood

Skin and subcutaneous tissue disorders

Rare: Alopecia (primarily body hair loss), hypertrichosis

Reproductive system and breast disorders

Very rare: Testicular pain and testicular swelling

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 5α-DHT.

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 54.9 cc at baseline to 42.1 cc) at Month 12 compared with a mean reduction of 0.5% (from 54.0 cc to 53.7 cc) 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 26.8 cc at baseline to 21.4 cc) in the *AVODART* group compared to a mean increase of 7.9% (from 26.8 cc to 27.5 cc) in the placebo group at Month 12. Reduction of the size of prostate leads to improvement of symptoms and a decreased risk for AUR and BPH-related surgery.

CLINICAL STUDIES:

AVODART monotherapy

AVODART 0.5 mg/day or placebo was evaluated in 4325 male subjects with moderate to severe symptoms of BPH who had prostates ≥30 cc 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. Results from pooled analyses of these study data are presented.

The most important clinical efficacy parameters were American Urological Association Symptom Index (AUA-SI), maximum urinary flow (Q_{max}) 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.

Q_{max} (maximum urine flow):

Mean baseline Q_{max} for the studies was approx 10 mL/sec (normal Q_{max} ≥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 Q_{max} seen during the first 2 years of double-blind treatment was maintained throughout an additional 2 years of open-label extension studies. Also, the reduction in prostate volume seen during the first 2 years of double-blind treatment was maintained thoughout 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) needs 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) needs 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.

***AVODART* in combination with the alpha-blocker tamsulosin:**

AVODART 0.5 mg/day, tamsulosin 0.4 mg/day or the combination of *AVODART* 0.5 mg plus tamsulosin 0.4 mg was evaluated in 4844 male subjects with enlarged prostates (greater than or equal to 30 cc) in a multicenter, double blind, parallel group study over 4 years. The primary efficacy endpoint at 2 years of treatment was the level of improvement from baseline in the international prostate symptom score (IPSS).

After 2 years of treatment, combination therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units. The adjusted mean improvements in symptom scores observed with the individual therapies were -4.9 units for *AVODART* and -4.3 units for tamsulosin. The adjusted mean improvement in flow rate from baseline was 2.4 mL/sec for the combination, 1.9 mL/sec for *AVODART* and 0.9 mL/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for the combination, -1.7 for *AVODART* and -1.5 for

tamsulosin.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for combination 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 *AVODART* monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6%; the difference between treatment groups was not significant ($p=0.18$ [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* .

Clinical progression was defined as a composite of worsening symptoms, (IPSS), and BPH-related events of AUR, incontinence, UTI, and renal insufficiency. Combination therapy was associated with a statistically significantly lower rate of clinical progression compared with tamsulosin ($p<0.001$, 44.1% risk reduction [95% CI: 33.6% to 53.0%]) after 4 years. The rates of clinical progression for combination therapy, tamsulosin, and *AVODART* were: 12.6%, 21.5%, and 17.8%, respectively.

The statistically significant adjusted mean improvement in symptom scores (IPSS) from baseline was maintained from year 2 to year 4. At 4 years, the adjusted mean improvements in symptom scores observed were -6.3 units for combination therapy, -5.3 units for *AVODART* monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in flow rate (Q_{max}) from baseline was 2.4 mL/sec for combination therapy, 2.0 mL/sec for *AVODART* monotherapy and 0.7 mL/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Q_{max} was statistically significantly greater with combination therapy at each 6-month assessment from Month 6 to Month 48 ($p<0.001$). Compared with *AVODART*, the adjusted mean improvement from baseline in Q_{max} was not statistically significantly different than with combination therapy ($p=0.050$ at Month 48).

Combination therapy was significantly superior ($p<0.001$) to tamsulosin monotherapy and to *AVODART* monotherapy for the improvement in health outcome parameters BII and BPH-related Health Status (BHS) at 4 years. The adjusted mean improvement in BII from baseline was -2.2 units for the combination, -1.8 for *AVODART* and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for *AVODART* and -1.1 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 4 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

Cardiac failure:

In this 4 year BPH 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%) (see section 4.4 Special Warnings and Special Precautions for Use).

In a 4-year chemoprevention comparison study 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 (the REDUCE study) there was a higher incidence of the composite term cardiac failure in subjects taking *AVODART* (30/4105, 0.7%) versus placebo (16/4126, 0.4%) for a relative risk estimate for time to first cardiac failure event of 1.91 [95% CI: 1.04, 3.50]. In a post-hoc analysis of concomitant alpha blocker use, there was 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 not taking *AVODART* and an alpha blocker concomitantly: *AVODART* and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), placebo and no alpha blocker (15/2727, 0.6%). No causal relationship between *AVODART* (alone or in combination with an alpha blocker) and cardiac failure has been established (see section 4.4 Special Warnings and Special Precautions for Use).

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 (the REDUCE study), 6,706 subjects had prostate needle biopsy 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). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81).

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). 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 (see section 4.4 Special Warnings and Special Precautions for Use).

The results of an epidemiological, population-based study (n=174,895) in community practice settings show that the use of 5-ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality (hazard ratio adjusted for competing risks: 0.85, 95% CI 0.72, 1.01) when compared with the use of alpha-blockers. Similar results were reported in an epidemiological study (n=13,892) of men with prostate cancer in the UK (adjusted hazard ratio for prostate cancer mortality for 5-ARI users versus non-users: 0.86; 95% CI 0.69, 1.06). A prospective cohort study, the Health Professional's Follow-up Study (n=38,058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69).

Effects on prostate specific antigen (PSA) and prostate cancer detection

In the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL *AVODART* treatment caused a decrease in mean serum PSA by approximately 50% after six months of treatment with a large variability (standard deviation of 30%) among patients. The PSA suppression observed at six months was similar in men who did or who did not develop biopsy-detectable prostate cancer during the study (see section 4.4 Special Warnings and Special Precautions for Use).

Incidence of breast cancer

In BPH monotherapy clinical trials, providing 3374 patient years of exposure to *AVODART*, there were 2 cases of male breast cancer reported in *AVODART* -treated patients, one after 10 weeks and one after 11 months of treatment and 1 case in a patient who received placebo. In subsequent clinical trials in BPH and 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 providing 17489 patient years exposure to *AVODART* and 5027 patient years exposure to *AVODART* and tamsulosin combination there were no reported breast cancer cases in any of the 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-ARIs (see section 4.4 Special Warnings and Special Precautions for Use). 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-ARIs compared with non-use was 1.08: 95% CI 0.62, 1.87).

The relationship between long term use of dutasteride and male breast cancer has not been established.

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%.

Elimination

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.

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 4.2 Posology and Method of Administration).

Hepatic impairment

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3 Contraindications). 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 4.2 Posology and Method of Administration and 4.4 Special Warnings and Special Precautions for Use).

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, butylhydroxytoluene (E321).

Capsule shell: gelatine; glycerol; titanium dioxide (E171); iron oxide yellow (E172); triglycerides, medium chain; lecithin.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

4 years.

6.4. Special Precautions for Storage

Do not store above 30°C.

6.5. Nature and Contents of Container

PVC/PVDC blister containing 10 soft gelatin capsules packed into containers of 30 and 90 capsules.

6.6. Instructions for Use/Handling (and disposal)

Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water (see 4.4 Special Warnings and Special Precautions for Use).

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