AVODART SOFT CAPSULES
Approved Package Insert

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

AVODART®
Soft Capsules

COMPOSITION:
Each soft gelatin capsule contains 0.5 mg dutasteride.
Anti-oxidant: Butylated hydroxytoluene (0.01 % m/m)

PHARMACOLOGICAL CLASSIFICATION: A 21.12 Hormone Inhibitors

PHARMACOLOGICAL ACTION:
Dutasteride is a dual inhibitor of 5α-reductase. It inhibits both type 1 and type 2, 5α-reductase isoenzymes which are responsible for the conversion of testosterone to 5α-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

Effects on DHT/Testosterone
The maximum effect of daily doses of AVODART on the reduction on DHT is dose dependent and is observed within 1 - 2 weeks. After 1 week and 2 weeks of daily dosing of AVODART 0.5 mg, median serum DHT concentrations were reduced by 85 % and 90 % respectively.

In BPH patients treated with 0.5 mg of dutasteride daily the median decrease in 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. This is an expected consequence of 5α-reductase inhibition and did not result in any known adverse events.

Dutasteride has no clinically significant effect on other androgens, hormones, thyroid stimulating hormone, thyroxine, total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, bone metabolism or bone density.

Pharmacokinetics:
Absorption
Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 - 3 hours.
Absolute bioavailability in man is approximately 60 %.
The bioavailability of dutasteride is not affected by food.

Distribution
Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride 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. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride

concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5 %.

Biotransformation
In vitro, dutasteride is metabolized by the human cytochrome P450 enzyme CYP450-3A4 to two minor monohydroxylated metabolites.
In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride).

Elimination
Dutasteride is extensively metabolized. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0 % to 15.4 % (mean of 5.4 %) of the administered dose is excreted as 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.
At therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks.
Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Linearity/non-linearity
Dutasteride pharmacokinetics can be described as first order absorption process and two parallel elimination pathways, one saturable (concentration dependent) and one non-saturable (concentration independent).
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 serum concentrations greater than 3 ng/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with terminal half-life of 3 to 5 weeks. At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower clearance dominates and the total clearance is linear and concentration independent.

Elderly
Dutasteride pharmacokinetics and pharmacodynamics 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. Exposure of dutasteride, represented by AUC and C_{max} values, was not statistically different when comparing age groups. No differences in drug effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose adjustment based on age is necessary.

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 adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment
The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see WARNINGS).

INDICATIONS:
Treatment of Benign Prostatic Hyperplasia (BPH).

CONTRA-INDICATIONS:

AVODART is contra-indicated in patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or any component of the preparation.
AVODART is contra-indicated for use by women.
AVODART is contraindicated for use in children.

WARNINGS:

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

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.

Effects on prostate specific antigen (PSA) and prostate cancer detection:
Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with AVODART and periodically thereafter.

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. Generally, a serum PSA concentration > 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA < 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). Therefore to interpret an isolated PSA value in a man treated with AVODART for 6 months or longer, PSA values should be doubled for comparison with normal ranges in untreated men.

This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. Any sustained increases in PSA levels while on AVODART should be carefully evaluated, including consideration of non-compliance to therapy with AVODART.

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 dutasteride therapy, no adjustment to its value is necessary.

DOSAGE AND DIRECTIONS FOR USE:

Adult males (including elderly)
The recommended dose of AVODART is one capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole (see WARNINGS).

AVODART may be taken with or without food.

Although an improvement may be observed at an early stage, treatment for at least 6 months may be necessary in order to assess objectively whether a satisfactory response to the treatment can be achieved.

Renal impairment
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see Pharmacokinetics.)

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. (See WARNINGS and Pharmacokinetics.)

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
The following drug related adverse events (with incidence ≥1 %) have been reported more commonly in the three Phase III placebo controlled studies on AVODART treatment compared to placebo:

Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
	Placebo (n= 2158)	AVODART (n= 2167)	Placebo (n= 1736)	AVODART (n= 1744)
Impotence	3%	6%	1%	2%
Altered (decreased) libido	2%	4%	<1%	<1%
Ejaculation disorders	<1%	2%	<1%	<1%
Gynaecomastia +	<1%	1%	<1%	1%

+ includes breast tenderness and breast enlargement

Interactions:
In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Phase II data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37 %) and diltiazem (44 %). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride.

A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10 times the recommended dose has been given to patients for up to six months), therefore no dose adjustment is necessary.

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Dutasteride neither inhibits human cytochrome P450 drug-metabolising enzymes *in vitro* nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs in vivo.

In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant interactions have been observed.

Although specific interaction studies were not performed with other compounds, approximately 90 % of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium

channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

A drug interaction study with tamsulosin or terazosin administered in combination with AVODART for two weeks showed no evidence of pharmacokinetic or pharmacodynamic interactions. A larger study in which dutasteride was co-administered with tamsulosin for up to 9 months showed that combination of AVODART with an alpha blocker was well tolerated.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In volunteer studies, single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for seven days have been administered without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to patients 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 cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate.

IDENTIFICATION:
Yellow, opaque, oblong, soft gelatin capsules with GX CE2 on one side printed in red.

PRESENTATION:
Blisters of opaque PVC/PVdC film-containing of 10 soft gelatin capsules, packed into cartons of 30 and 90 capsules.

STORAGE INSTRUCTIONS:
KEEP OUT OF REACH OF CHILDREN.
Store below 30 ºC.

REGISTRATION NUMBER: 37/21.12/0282

NAME AND BUSINESS ADDRESS OF APPLICANT:
GlaxoSmithKline South Africa (Pty) Ltd
57 Sloane Street
Bryanston, 2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT: 09 May 2003