SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

AVODART Soft Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each soft gelatin capsule contains 0,5 mg dutasteride.

Anti-oxidant: Butylated hydroxytoluene (0,01 % *m/m*)

Sugar Free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

An oblong, opaque, dull-yellow, soft gelatin capsule with GX CE2 on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Treatment of Benign Prostatic Hyperplasia (BPH).

Treatment in combination with an alpha-1 adrenergic blocker may have additional symptomatic benefit, but combination therapy does not lead to more reduction in prostate size, compared to AVODART monotherapy alone.

4.2 Posology and method of administration:

Posology:

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 and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa (see section 4.4).

Leaking capsules should be discarded.

AVODART may be taken with or without food.

Treatment for at least 6 months may be necessary in order to assess objectively whether a satisfactory response to the treatment has been 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 section 5.2).

Hepatic impairment:

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (see section 4.4 and 5.2).

4.3 Contraindications:

AVODART is contraindicated in patients with a known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or any component of the preparation.

AVODART is contraindicated for use by women (see section 4.6).

AVODART is contraindicated for use in children.

4.4 Special warnings and 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, there was a non-significant difference in the incidence of prostate cancer compared to placebo. 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 chemo prevention study (REDUCE), a low rate of new prostate cancers was 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 (5α-reductase inhibitors), (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).

Prostate specific antigen (PSA) :

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 sustained increases from lowest PSA level while on AVODART may signal the presence of prostate cancer or non-compliance to therapy with AVODART.

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 is necessary.

Digital rectal examination, as well as other evaluations including PSA 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 approximately doubled among subjects taking the combination of AVODART and an alpha blocker, than it was among subjects not taking the combination. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established.

Patients with cardiovascular risk factors should only use a concomitant alpha blocker with great care. When AVODART is used in combination with alpha blockers, the frequency of adverse events is increased. 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 dutasteride (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. Medical practitioners 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 and children 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.

Method of administration

Capsules should be swallowed whole. Leaking capsules may cause mouth, throat and oesophageal irritation and should be discarded.

AVODART is transmitted to women during sexual intercourse. Women in their fertile years, should use adequate contraceptive measures.

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 in patients with liver disease. See section 4.2 and 5.2

4.5 Interactions with other medicines and other forms of interaction:

In vitro 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.

When co-administered with the CYP3A4 inhibitors verapamil, the clearance of dutasteride was reduced by 37 % and in combination with diltiazem by 44 %. No decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with AVODART. The clinical significance of this interaction has not been formally studied.

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Dutasteride neither inhibits human cytochrome P450 medicine-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, phenprocoumon, diazepam, or phenytoin from plasma protein nor do these model compounds displace dutasteride.

Compounds that have been tested for medicine interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant interactions have been observed.

Specific interaction studies were not performed with other compounds. However, approximately 90 % of the subjects in large Phase III studies receiving AVODART were taking other medicines concomitantly. No clinically significant adverse interactions were observed in clinical trials when AVODART 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 (such as sildenafil, tadalafil), and quinolone antibiotics.

An interaction study with tamsulosin or terazosin administered in combination with AVODART for two weeks showed no evidence of pharmacokinetic or pharmacodynamic interactions.

4.6 Fertility, pregnancy and lactation:

Fertility:

AVODART reduces fertility, libido and sperm count. In individual cases decreases in sperm count were 90 %. AVODART reduces sperm volume and sperm motility which may persist after discontinuation of treatment.

Pregnancy:

AVODART is contraindicated for use by women. In animals, dutasteride inhibited the development of genitals of male foetuses.

Dutasteride is transmitted to women during sexual intercourse. Adequate contraceptive measures (condoms) should be used when having sexual intercourse with women in their fertile years.

Lactation:

It is not known whether dutasteride is excreted in the breast milk.

4.7 Effects on the ability to drive and use machines:

AVODART, mainly when used in combination with alpha-$_1$ blockers may cause dizziness. Patients should be cautioned about their ability to drive and operate machinery when receiving combination therapy.

4.8 Undesirable effects:

Clinical Trial Data:

The following treatment related adverse events have been reported more commonly in the Phase III placebo-controlled studies on AVODART treatment compared to placebo. Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000) including isolated reports.

MedDRA System organ class	**Adverse reaction(s)**	**Frequency**
Nervous system disorders	Dizziness (mainly in combination with alpha-1 blockers)	Uncommon
Reproductive system and breast disorders	Impotence	Common

	Altered (decreased) libido	Common
	Ejaculation disorders	Common
	Breast disorders including breast tenderness and breast enlargement (gynaecomastia)	Common

Post-marketing Data:

MedDRA System organ class	**Adverse reaction(s)**
Immune system disorders	Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema
Psychiatric disorders	Depressed mood
Skin and subcutaneous tissue disorders	Alopecia (primarily body hair loss), hypertrichosis
Reproductive system and breast disorders	Testicular pain and testicular swelling

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

There is no specific antidote for dutasteride therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 21.12 Hormone Inhibitors

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:

After 1 week and 2 weeks of daily dosing of dutasteride 0,5 mg, median serum DHT concentrations were reduced by 85 % and 90 % respectively.

In Benign Prostatic Hyperplasia (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 response to 5α-reductase inhibition**.**

5.2 Pharmacokinetic properties:

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 toplasma 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 metabolised 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) was detected.

Elimination: Dutasteride is extensively metabolised. 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 medicine-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 medicine 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 section 4.4).

5.3 Preclinical safety data:

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule contents: butylated hydroxytoluene (0,01% m/m) as the anti-oxidant and mono-di-glycerides of caprylic/capric acid.

***Capsule shell*:** gelatin, glycerol , titanium dioxide, yellow iron oxide, medium chain triglycerides and lecithin as capsule lubricants.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

48 months.

6.4 Special precautions for storage:

Store at or below 30 °C.

6.5 Nature and contents of container:

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

6.6 Special precautions for disposal and other handling:

Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsule the contact area should be washed immediately with soap and water *(*See section 4.4 and 4.7)

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

37/21.12/0282

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