Avodart™

Dutasteride

1. NAME OF THE MEDICINAL PRODUCT

AVODART*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral use contains 0.5 mg dutasteride.
For excipients, see 6.1 List of Excepient.

3. PHARMACEUTICAL FORM

Capsules: dull yellow in colour, opaque, oblong soft gelatin capsules with GX CE2 printed on one side in red ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

AVODART treats and prevents progression of Benign Prostatic Hyperplasia (BPH) through alleviating symptoms, reducing prostate size (volume), improving urinary flow rate and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery.

4.2. Posology and Method of Administration

Adult males (including elderly)

The recommended dose is one capsule (0.5 mg) take orally once a day. Capsules should be swallowed whole. **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 5.2 Pharmacokinetic Properties)

Hepatic impairment

The effect o hepatic impairment on dutasteride pharmacokinetics has not been studied. (See 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties).

4.3. Contra-indications

AVODART is contra-indicated in patients with known hypersensitivity to dutasteride, other 5a-reductase inhibitors, or any component of the preparation. (See 6.1 List of Excipients).
AVODART is contraindicated for use in women and children (see 4.6 Use during pregnancy and Lactation).

4.4 Special Warnings and Special Precaitions for Use

Dutasteride is absorbed through the skin, therefore, women and children must avoid contact with leaking capsules (see 4.6 Use During Pregnancy and Lactation). 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 metabolized 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 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic Properties).

Effect 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 dutasteride 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 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 dutasteride does not exclude a diagnosis of prostate cancer.

AVODART causes a decrease in serum PSA levels by approximately 40% following 3 months of treatment and 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 for interpretation of serial PSAs in a man taking **AVODART**, a new baseline PSA concentration should be established after 3 to 6 months of treatment, and this new value should be used to assess potentially cancer-related change in PSA. 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.

Information fo patients

Phisicians should instruct their patients to read the patient information leaflet before starting therapy with **AVODART** and to re-read it upon prescription renewal for new information regarding the use of **AVODART**.

Physicians should inform patients that ejaculate volume might be decreased in some patients during treatment with **AVODART**. This decrease doesn’t appear to interfere with normal sexual function. In clinical trials, impotence and decreased libido, considered by the investigator to be drug-related, occurred in a small number of patients treated with **AVODART** or placebo.

Pediatric use

AVODART is not indicated for use in pediatric population. Safety and effectiveness in the pediatric population have not been established.

Geriatric use

Of 2,167 male subjects treated with **AVODART** in 3 clinical studies, 60% were 65 and over 15% were 75 and over. No overall differences in safety and efficacy were observed between these

subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients.

CNS toxicity

In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non specific, reversible, centrally-mediated toxicity, without associated histopathological changes at exposure 425-and 315-fold the expected clinical exposure (of parent dug), respectively.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P_{450} isoenzyme CYP3A4. Therefore blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4. Care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors.

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 metabolized by human cytochrome P_{450} isoenzymes CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Dutasteride neither inhibits human cytochrome P450 drug-metabolizing 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 subject 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.

4.6. Use during Pregnancy and Lactation

Pregnancy

Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because pre clinical data suggest that the supression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman

exposed to dutasteride.

Lactation

It is not known whether dutasteride is excreted in breast milik. **AVODART** is not indicated for use in women.

4.7. Effects on Ability to Drive and Use Machines

Based on the pharmacokinetic and 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

The following investigator judged drug related adverse events (with incidence ³1%) 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 1 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

4.9. Overdose

In volunteer studies single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for 7 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, the long half-life dutasteride into consideration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

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

Effect 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** 0.5mg, 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 5a-reductase inhibition and did not result in any known adverse events.

CLINICAL STUDIES

Dutasteride 0.5 mg/day or placebo was evaluated in 4325 male subjects with enlarged prostates (greater than 30 cc) in three primary efficacy 2-year multicenter, placebo-controlled, double-blind studies.

In men with BPH, **AVODART** treats and prevents disease progression by reducing the risk of both acute urinary retention (AUR) and the need for surgical intervention (SI) and by providing statistically significant improvement of lower urinary tract symptoms (LUTS), maximum urinary flow rate (Qmax) and prostate volume relative to placebo. These improvements in LUTS, Qmax and prostate volume were seen through to 24 months.

5.2. Pharmacokinetic Properties

Absorption

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 0.5mg dose, peak serum concentrations of dutasteride occur within 1-3 hours. Absolute bioavailability in man is approximately 60% relative to a 2 hours intravenous infusion. 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 CYP_{450}-3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP_{450}-1A2, 2C9, 2C19 or 2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydrodutasteride) and 2 minor metabolites (6,4'-dihydrodutasteride and 15-hydrodutasteride), as assessed by mass spectrometric response, have been detected. The five human serum metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

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 concentration (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 3ng/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. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old group which encompasses the age of most men with BPH. 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 4.4 Special Warnings and Special Precautions for Use).

5.3 Preclinical Safety Data

At exposure greatly in excess of those at the clinical dose, reversible, non specific CNS related effects were seen in rats (425-fold) and dogs (315-fold).

Other toxicity findings were consistent with the pharmacological activity of 5AR inhibition. In male rats and dogs, these included effects on accessory reproductive organs and, in male rats, a reversible decrease in fertility. This is considered to have no clinical relevance as there was no effect on sperm development, concentration or motility. Feminisation of the external genitalia was noted in male foetuses of female rats and rabbits orally dosed with dutasteride. However, intravenous administration of dutasteride to pregnant Rhesus monkeys during embryofoetal development at doses of up to 2010 ng/animal/day did not produce adverse maternal or foetal toxicity. This dose represents a multiple of at least 186-fold (ng/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100% absorption) from a dutasteride-treated man. Dutasteride was not genotoxic in a wide range of mutagenicity tests. In a carcinogenicity study in rats, there was an increase in benign interstitial cell tumours in the testid at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Capsule contents : monodiglycerides of caprylic/capric acid; butylated hydroxytoluene
Capsule shell: gelatin; glycerol; titanium dioxide (E171, CI 77891); iron oxide yellow (E172, CI 77492); red printing ink containing polyvinyl acetate phthalate, polyethylene glycol, propylene glycol and iron oxide red (E172, CI 77491) as the colourant; Medium chain triglycerides and lecithin as capsule lubricants.

6.2. Incompatibilities

Not applicable

6.3. Special Precautions for Storage

Do not store above 30°C

6.4. Nature and Contents of Container

Blisters of opaque PVC/PVDC film containing 10 capsules, packed into cartons of 30 and 90 capsules.

6.5. Instructions for Use/Handling

Dutasteride is absorbed through the skin, therefore, women and children must avoid contact with leaking capsules (see 4.6 Use During Pregnancy and Lactation). If contact is made with leaking capsules the contact area should be washed immediately with soap and water.

Package Insert Leaflet revised December 2002, version 2.0.

HARUS DENGAN RESEP DOKTER

Avodart, 3 blister @ 10 Soft Capsules
Avodart, 9 blister @ 10 Soft Capsules

Manufactured by
Cardinal Health France 404, Beinheim, France
Packed by
Cardinal Health Germany 405 GmbH, Germany

Imported by
PT. SmithKline Beecham Pharmaceuticals
Bogor, Indonesia

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