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AVODART

GlaxoSmithKline

Dutasteride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral use contains 0.5 mg dutasteride (see List of Excipients).

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

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.

In addition, AVODART in combination with the alpha-blocker tamsulosin, treats and prevents progression of benign prostatic hyperplasia (BPH) by reducing prostate size, alleviating symptoms and improving urinary flow (see Clinical Studies).

Dosage and 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.

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, 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 Precautions and Pharmacokinetics).

Contraindications

AVODART is contraindicated in patients with known hypersensitivity to dutasteride, other 5 –alpha-reductase inhibitors, or any component of the preparation (see List of Excipients).

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

Warnings and Precautions

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.

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 Dosage and Administration and Pharmacokinetics).

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 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 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.

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 metabolized by human cytochrome P450 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 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.

Pregnancy and Lactation

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 clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

Pregnancy

Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because pre-clinical data suggests that the suppression 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 milk.

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.

Adverse Reactions

Clinical Trial Data

AVODART Monotherapy

The following investigator-judged 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%
Breast disorders+	<1%	1%	<1%	1%

+ includes breast tenderness and breast enlargement

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

AVODART and Tamsulosin Combination Therapy

The following investigator-judged drug-related adverse events (with an incidence of greater than or equal to 1%) have been reported in the 2 year analysis of 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.

(See chart on next page)

Postmarketing Data

Adverse drug reactions are listed below by system organ class and frequency.

Frequencies are defined as:

very common: ≥1 in 10
common: ≥1 in 100 and <1 in 10
uncommon: ≥1 in 1,000 and <1 in 100
rare: ≥1 in 10,000 and <1 in 1,000
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 reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Dutasteride is a dual inhibitor of 5 alpha-reductase. It inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to 5 alpha-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 5 alpha-reductase inhibition and did not result in any known adverse events. See Table.

Pharmacokinetics

Absorption

Dutasteride is administered orally in solution as a soft gelatin capsule. 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% relative to a 2 hour 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 (Css) 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 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP1A2, CYP2C9, CYP2C19 or CYP2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites

Adverse event	Incidence during year 1 of treatment			Incidence during year 2 of treatment		
	AVODART + Tamsulosin (n=1610)	*AVODART* (n=1623)	Tamsulosin (n=1611)	*AVODART* + Tamsulosin (n=1424)	*AVODART* (n=1457)	Tamsulosin (n=1468)
Impotence	7%	5%	3%	1%	1%	<1%
Altered (decreased) libido	5 %	4%	3%	<1%	<1%	<1%
Ejaculation disorders	9%	2%	3%	<1%	<1%	<1%
Breast disorders†	2%	2%	<1%	<1%	1%	<1%
Dizziness	1%	<1%	1%	<1%	<1%	<1%

† includes breast tenderness and breast enlargement

(4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), 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 mate6 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 Cmax 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 Warnings and Precautions).

Clinical Studies

AVODART monotherapy

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, and LUTS and Qmax continued to improved for a further 2 years in open-label extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open-label extension studies.

AVODART and tamsulosin combination therapy

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 2 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.

Pre-clinical Safety Data

At exposures 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 5 alpha-reductase 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 testis 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.

PHARMACEUTICAL PARTICULARS

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 iron oxide red (E172, CI 77491) as the colourant, polyvinyl acetate phthalate, polyethylene glycol and propylene glycol.

Medium chain triglycerides and lecithin as capsule lubricants.

Incompatibilities

Not applicable.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store above 30oC.

Nature and Contents of Container
Blisters of opaque PVC/PVDC film, packed into cartons.

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

Not all presentations are available in every country.

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