Approved Professional Information for Medicines for Human Use

PRODART 0,5 mg

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

PRODART 0,5 mg soft gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains 0,5 mg dutasteride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft gelatin capsules.

A dull yellow, opaque colour, oblong shape, soft gelatin capsule containing clear transparent liquid imprinted with “DUTA 05” using black coloured edible ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Benign Prostatic Hyperplasia (BPH).

4.2 Posology and method of administration

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Adult males (including elderly)

The recommended dose of PRODART is one capsule (0,5 mg) taken orally once a day.

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.

Special populations

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).

Method of administration:

Oral use. The capsules should be swallowed whole (see section 4.4).

PRODART may be taken with or without food.

4.3 Contraindications

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- PRODART is contraindicated in patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or to any of the excipients listed in 6.1.
- PRODART is contraindicated for use by women.
- PRODART is contraindicated for use in children.

4.4 Special warnings and precautions for use

Leaking capsules

Dutasteride as in PRODART is absorbed through the skin, therefore, women and children must avoid contact with leaking capsules (see section 4.3). If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

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 benign prostatic hyperplasia (BPH) prior to initiating therapy with PRODART 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 PRODART does not exclude a diagnosis of prostate cancer.

PRODART causes a decrease in serum PSA levels by approximately 50 %, after 6 months, in patients with BPH, even in the presence of prostate cancer.

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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 PRODART 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 PRODART should be carefully evaluated, including consideration of non-compliance to therapy with PRODART.

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 PRODART. If physicians 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.

Cardiovascular adverse events

In a reported two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was marginally higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. However, the incidence of cardiac failure in these reported trials were lower in all actively treated groups compared to the placebo group, and other data available for dutasteride or alpha-blockers do not support a conclusion on increased cardiovascular risks.

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Breast neoplasia

Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple changes.

Hepatic impairment

PRODART was not studied in patients with liver disease and 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 exercised in the administration of dutasteride as in PRODART to patients with mild to moderate hepatic impairment (see section 4.2 and section 5.2).

Risk of non-alcoholic fatty liver disease (NAFLD)

From the available data it is has been observed that androgen deficiency is a risk factor for non-alcoholic fatty liver disease (NAFLD). As with other 5α-reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone. Consequently, there is a risk that patients receiving dutasteride may develop NAFLD.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on the pharmacokinetics of dutasteride

Use together with CYP3A4 inhibitors:

In vitro drug metabolism studies show that dutasteride as in PRODART is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore,

blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Studies showed a decrease in clearance of dutasteride as in PRODART 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 as in PRODART, 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*.

Long-term combination of dutasteride, as in PRODART, with medicines that are potent inhibitors of the enzyme CYP3A4 (e.g. ritonavir, indinavir, nefazodone, itraconazole, ketoconazole administered orally), may increase serum concentrations of dutasteride.

Administration of 12 g colestyramine on hour after a 5 mg single doses of dutasteride as in PRODART, did not affect the pharmacokinetics of dutasteride.

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Effects of PRODART on the pharmacokinetics of other medicines

In vitro studies demonstrate that dutasteride as in PRODART, does not displace warfarin, diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Dutasteride has no effect on the pharmacokinetics of digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P- glycoprotein.

Medicines that have been tested for 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 medicines, approximately 90 % of the subjects receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed 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.

An interaction study with tamsulosin or terazosin administered in combination with dutasteride 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 dutasteride with an alpha blocker was well tolerated.

4.6 Fertility, pregnancy and lactation

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PRODART is contraindicated for use in women.

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 section 4.4). Small amounts of dutasteride have been recovered from the semen in subjects receiving PRODART 0,5 mg day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy).

When a patient's partner is or may potentially be pregnant, it is recommended that the patient avoids exposure of his partner to semen by the use of a condom.

Breastfeeding

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

Fertility

Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men (see section 5.1). The possibility of reduced male fertility cannot be excluded.

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4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties of dutasteride, treatment with PRODART would not be expected to interfere with the ability to drive or operate machinery.

4.8 Undesirable effects

The frequency of adverse reactions reported with PRODART are summarised in the tables below according to the MedDRA system organ class (SOC).

Table 1: Tabulated list of adverse reactions from clinical trials

System organ class	**Adverse reaction**	**Frequency**	
		Year 1	Year 2
Reproductive system and breast disorders	Impotence	frequent	frequent
	Altered (decreased) libido	frequent	less frequent
	Ejaculation disorders	frequent	less frequent
	Gynaecomastia*	frequent	frequent

*Includes breast tenderness and breast enlargement

Table 2: Tabulated list of adverse reactions from post-marketing data

System organ class	**Adverse reaction**	**Frequency**
Immune system disorders	Allergic reactions including rash, pruritus, urticaria, localised oedema, and angioedema	unknown
Psychiatric disorders	Depression	unknown
Skin and subcutaneous tissue disorders	Alopecia (primarily body hair loss), hypertrichosis	less frequent
Reproductive system and breast disorders	Testicular pain and swelling	unknown

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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 as in PRODART, therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 21.12 Hormone inhibitors.

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors

ATC code: G04C B02

Mechanism of 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 dutasteride on the reduction on DHT is dose dependent and is observed within 1 - 2 weeks. After 1 week and 2 weeks

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of daily dosing of dutasteride 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.

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 45 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 %).

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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 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.

Special populations

Elderly

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In clinical studies, exposure of dutasteride, represented by AUC and Cmax values, was not statistically different when comparing age groups of 24 and 87 years old. 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 93 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

butylated hydroxy toluene (0,01 % m/m)

glycerol monocrylocaprate

Capsule shell:

ferric oxide yellow

gelatin

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glycerine

glyceryl monocaprylocaprate

purified water

titanium dioxide

printing ink (consisting of black iron oxide, hypromellose, isopropyl alcohol, purified water, propylene glycol).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 ºC.

6.5 Nature and contents of container

Capsules are packed in white opaque PVC/PVDC and Aluminium foil blister strips of 10, which are further packed in printed cartons, in pack sizes of 30 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

PRODART is absorbed through the skin, therefore contact with leaking capsules must be avoided. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

52/21.12/1015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 May 2022

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10. DATE OF REVISION OF THE TEXT

24 March 2023