Proposed Professional Information for ZEDRAST

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZEDRAST 0,5 mg soft capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0,5 mg dutasteride.

Preservatives: 0,2 % *m/m* methyl hydroxybenzoate and 0,03 % *m/m* propyl hydroxybenzoate.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft.

Opaque, yellow, oblong shaped soft gelatine capsules containing a clear, colourless to slightly yellowish oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZEDRAST is indicated for the 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 ZEDRAST monotherapy alone.

4.2 Posology and method of administration

Posology

Adult males (including elderly)

The recommended dose of ZEDRAST 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.

ZEDRAST may be taken with or without food.

Although an improvement may be observed at an early stage, treatment for at least six 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 sections 4.4 and 5.2).

Method of administration

For oral administration. The capsule should be swallowed whole.

4.3 Contraindications

ZEDRAST is contraindicated in:

- Patients with hypersensitivity to dutasteride, other 5α-reductase inhibitors or to any of the excipients of ZEDRAST.

- Women (see section 4.6).
- Children and adolescents younger than 18 years (see section 4.4).
- Patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Careful benefit risk assessment is recommended before prescribing combination therapy (due to the potential increased risk of adverse events, including cardiac failure), as well as consideration of alternative treatment options including monotherapies (see section 5.2).

Prostate cancer and high grade tumours

Male patients taking ZEDRAST should be evaluated for prostate cancer on a regular basis (see sections 4.8 and 5.1). A study conducted in patients with a high risk for prostate cancer has shown a higher incidence of Gleason 8 – 10 prostate cancers in those receiving dutasteride, in comparison to those receiving a placebo. The relationship between ZEDRAST and Gleason 8 – 10 prostate cancers is uncertain, therefore regular evaluations are recommended.

Prostate specific antigen (PSA)

Prior to initiating therapy with ZEDRAST and periodically thereafter, digital rectal examination, as well as other evaluations for prostate cancer should be performed on patients.

The serum PSA concentration is an important component in the detection of prostate cancer. Further examination and consideration of prostate biopsy is usually required with a serum PSA concentration > 4 ng/mL (Hybritech). A baseline PSA < 4 ng/mL in patients taking ZEDRAST does however not exclude a diagnosis of prostate cancer.

ZEDRAST causes a decrease in mean serum PSA levels by approximately 50 % after 6 months of treatment. Despite individual variation, the reduction in PSA values of approximately 50 % was observed over the entire range of baseline PSA values (1,5 to 10 ng/mL). In patients receiving

ZEDRAST, a new PSA baseline should be established after six months of treatment and the PSA values monitored regularly thereafter.

After a new baseline has been established, treatment with ZEDRAST does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer.

Even if the values are still within the normal range for patients not taking a 5α-reductase inhibitor, any sustained increases from lowest PSA level in patients taking ZEDRAST may be an indication of prostate cancer or nonadherence to the therapy and should be carefully evaluated. The previous PSA values should be used in comparison when interpreting the PSA value of a patient taking ZEDRAST.

The total serum PSA levels return to baseline within 6 months of discontinuing ZEDRAST. Treatment with ZEDRAST does not influence the ratio of free to total PSA and in patients taking ZEDRAST, no adjustment to the value of the free PSA is necessary when used as an aid in the detection of prostate cancer.

Cardiovascular adverse events

Studies have shown a marginally higher incidence of cardiac events (such as cardiac failure and congestive cardiac failure) in men taking a combination of dutasteride and an α-blocker (primarily tamsulosin), in comparison to men not taking the combination. The incidence of cardiac failure was however still lower in men taking the combination, than in those not taking either of the medicines. A conclusion on the increase in cardiovascular risk is not supported by other data available on dutasteride and α-blockers (see section 5.1).

Breast neoplasia

During both clinical trials and the post-marketing period, there have been reports of breast cancer in men taking dutasteride. Epidemiological studies however do not support the increase in risk of

developing male breast cancer while taking a 5α-reductase inhibitor (see sections 4.8 and 5.1). Caution is recommended and patients must be instructed to report any changes in breast tissue, such as lumps or nipple discharge, while taking ZEDRAST.

Leaking capsules

ZEDRAST contains dutasteride, which is absorbed through the skin. Women, children and adolescents must avoid contact with leaking capsules (see section 4.3). In the event of contact with a leaking capsule, the contact area should immediately be washed with soap and water. ZEDRAST should not be chewed or opened as contact with the capsule may result in irritation of the oropharyngeal mucosa.

Hepatic impairment

No studies have been done regarding the use of ZEDRAST in patients with hepatic disease. ZEDRAST undergoes extensive metabolism and has a terminal half-life of 3 to 5 weeks. Caution is therefore advised in the administration of ZEDRAST to patients with mild to moderate hepatic impairment (see sections 4.2 and 5.2).

Paediatric population

The use of ZEDRAST is contraindicated in children and adolescents (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P3A4 (CYP3A4) and/or P-glycoprotein-inhibitors

ZEDRAST is primarily eliminated via metabolism, which is catalysed by the human cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Although no interaction studies have been performed with potent CYP3A4 inhibitors, respective increases of 1,6 to 1,8 times were seen in dutasteride concentrations when treated concurrently with verapamil or diltiazem during pharmacokinetic studies. Verapamil and diltiazem are both moderate inhibitors of CYP3A4 and P-glycoprotein and respectively caused 37 % and 44 % decrease in clearance of dutasteride. No decrease in

clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with ZEDRAST. The clinical significance of this interaction has not been formally studied.

The serum concentrations of ZEDRAST may be increased in long-term co-administration with potent CYP3A4 inhibitors, such as ritonavir, indinavir, itraconazole and oral ketoconazole. The increase in ZEDRAST exposure does not result in additional 5α-reductase inhibition. Should adverse events be noted, a reduction in the frequency of ZEDRAST doses can be considered. The long half-life of ZEDRAST is extended when co-administered with CYP450 enzyme inhibitors and a new steady state may take as much as 6 months of concurrent therapy to reach.

No dose adjustment of ZEDRAST is required in the concomitant administration with CYP450 inhibitors.

Colestyramine

The pharmacokinetics of ZEDRAST is not affected by the use of colestyramine when administered one hour apart.

Effects of ZEDRAST on the pharmacokinetics of other medicines

ZEDRAST does not induce nor inhibit the CYP2C9 enzyme or the transporter P-glycoprotein and therefore has no influence on the pharmacokinetics of warfarin and digoxin. *In vitro* studies indicate that warfarin, phenprocouman, diazepam and phenytoin are not displaced from plasma protein by ZEDRAST.

In vitro studies further demonstrate that ZEDRAST does not inhibit the enzymes CYP1A2, CYP2C9, CYP2D6 and CYP2C19. 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*.

As indicated by interaction studies, ZEDRAST has no clinically significant effect on the

pharmacokinetics or pharmacodynamics of tamsulosin, terazosin, warfarin, digoxin and colestyramine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ZEDRAST is contraindicated in women (see section 4.3).

In animals, dutasteride inhibited the development of genitals of male foetuses.

ZEDRAST is a 5α-reductase inhibitor, inhibiting the conversion of testosterone to dihydrotestosterone. Small amounts of dutasteride may be present in the semen of men taking ZEDRAST (see section 5.2). The risk of adverse effects on the foetus is unknown if the mother is exposed to semen of a patient taking ZEDRAST (the risk of which is greatest during the first 16 weeks of pregnancy). Caution is advised when the partner of a patient taking ZEDRAST is or may potentially be pregnant. It is recommended that the patient avoids exposure of his partner to semen by use of a condom.

Breastfeeding

It is unknown whether ZEDRAST is excreted into breast milk.

Fertility

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

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.

4.7 Effects on ability to drive and use machines

ZEDRAST, mainly when used in combination with alpha-1 blockers, may cause dizziness (see section 4.8). Based on the pharmacodynamic properties of ZEDRAST, no influence on the ability to drive or operate machinery is expected. Caution is however advised before driving a vehicle or operating machinery until the effects of ZEDRAST are known.

4.8 Undesirable effects

The following undesirable effects have been reported during clinical trials with dutasteride as monotherapy

Nervous system disorders

Less frequent: dizziness (mainly in combination with alpha-1 blockers)

Cardiac disorders

Less frequent: cardiac failure (composite term)[a]

[a]Cardiac failure composite term comprised of congestive cardiac failure, cardiac failure, left ventricular failure, acute cardiac failure, cardiogenic shock, acute left ventricular failure, right ventricular failure, acute right ventricular failure, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.

Reproductive system and breast disorders

Frequent: impotence*, altered (decreased) libido*, ejaculation disorders (including decreased semen volume)*, breast disorders (including breast tenderness and breast enlargement)

*These adverse events are associated with both monotherapy and in combination with tamsulosin. These adverse events may persist after treatment discontinuation. The role of ZEDRAST in this persistence is unknown.

Post-marketing data:

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 swelling.

Other data

There have been studies reporting a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride-treated men (see section 4.4).

There have also been reports of male breast cancer in clinical trials and post-marketing use (see section 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms of overdose

In volunteer studies, single daily doses of dutasteride up to 40 mg daily (80 times the therapeutic dose) administered for 7 days, did not result in significant safety concerns. In clinical studies, the administration of 5 mg daily for 6 months had no additional adverse effects in comparison to those seen at therapeutic doses of 0,5 mg daily.

Management of overdose

No specific treatment of overdosage with ZEDRAST can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

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 isoenzymes. Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5α-reductase isoenzymes, which are responsible for the conversion of testosterone to DHT. DHT is the androgen mainly responsible for hyperplasia of glandular prostatic tissue.

Dutasteride as monotherapy

Effects of dutasteride on DHT/testosterone

The maximum effect of daily doses of ZEDRAST 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 ZEDRAST 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 unexpected 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

Peak serum concentration occurs within 1 – 3 hours, following oral administration of a single 0,5 mg dutasteride dose. The absolute bioavailability is approximately 60 %. Concomitant food administration has no effect on the oral bioavailability of dutasteride.

Distribution

Dutasteride is highly bound to plasma proteins (> 99,5 %) and has a large volume of distribution (300 – 500 L). Serum concentrations achieve 65 % of steady state concentrations after 1 month, and approximately 90 % after 3 months following daily dosing with dutasteride. After 6 months of 0,5 mg dutasteride taken daily, steady state serum concentrations of approximately 40 ng/mL are achieved. Dutasteride can be detected in semen (see section 4.6) and achieved steady state after 6 months. Dutasteride partitioning from serum into semen averaged at 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).

Elimination

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0,5 mg/day to steady state in humans, 1,0 % – 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 – 5 weeks. Serum concentrations remain detectable (greater than 0,1 ng/mL) for up to 4 – 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

Dutasteride pharmacokinetics and pharmacodynamics were evaluated in 36 healthy male subjects between 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} value, 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 the 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

Glycerol monocaprylocaprate (type I).

Capsule shell:

Ferric oxide yellow (colourant)

Gelatine

Glycerol

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Titanium dioxide (colourant).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strip in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium-aluminium blister strips containing 6 soft gelatine capsules, packed in an outer container.

Pack size: 6

OR

Opaque PVC/PVDC and aluminium blister strips containing 10 soft gelatine capsules, packed in an outer container.

Pack sizes: 10 and 30.

6.6 Special precautions for disposal and other handling

Dutasteride is absorbed through the skin. Women, children and adolescents must avoid contact with leaking capsules. In the event of contact with a leaking capsule, the contact area should immediately be washed with soap and water (see section 4.4).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building A, Second Floor

22 Karee Street

Centurion 0157

South Africa

Tel: 012 748 6400

8. REGISTRATION NUMBER

54/21.12/0491

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 15 June 2021.

10. DATE OF REVISION OF THE TEXT

26 May 2026