PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ACTASVO 0,5 mg soft 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 capsules

Oblong, opaque and yellow soft gelatin capsules containing an oily and yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Benign Prostatic Hyperplasia (BPH).

4.2 Posology and method of administration

Posology

Adult males (including elderly)

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

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

ACTASVO 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.

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 4.3; section 4.4 and section 5.2). In patients with severe hepatic impairment, the use of dutasteride is contraindicated (see section 4.3).

Paediatric population

The use of ACTASVO in children is contraindicated (see section 4.3).

Method of administration

Capsules for oral use.

4.3 Contraindications

The use of ACTASVO is contraindicated in:

- Hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, soya or any of the excipients (see section 6.1).
- women and children.
- patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Leaking capsules

Dutasteride 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.

Hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. ACTASVO should be administered with caution in patients with mild to moderate hepatic impairment because dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks (see section 5.2).

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 ACTASVO 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. Medical practitioners should be aware that a baseline PSA < 4 ng/ml in patients taking ACTASVO does not exclude a diagnosis of prostate cancer.

ACTASVO causes a decrease in serum PSA levels by approximately 50 %, after 6 months of treatment, 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 is observed over the entire range of baseline PSA value (1,5 to 10 ng/ml). Therefore, to interpret and isolated PSA value in a man treated with ACTASVO for 6

months or longer, PSA values should be doubled for comparison with normal ranges in untreated men.

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

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 ACTASVO. 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.

Prostate cancer and high grade tumours

The results of a study to investigate the effect of dutasteride 0,5 mg daily on patients with a high risk for prostate cancer revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men. The relationship between dutasteride and Gleason 8 – 10 prostate cancers is not clear. Thus, men taking ACTASVO should be regularly evaluated for prostate cancer.

Breast neoplasia

Male breast cancer has been reported in men taking dutasteride. Patients should therefore be instructed to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Cardiovascular adverse events

It is documented that 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 marginally higher among subjects taking the combination of ACTASVO and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination.

However, the incidence of cardiac failure in these trials was 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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on the pharmacokinetics of dutasteride

Dutasteride is mainly eliminated via metabolism. Dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4. Concomitant use of ACTASVO with the CYP3A4 inhibitors verapamil and diltiazem have shown a decrease in the clearance of dutasteride. In contrast, no decrease in clearance has been reported when amlodipine, another calcium channel antagonist, was co-administered with ACTASVO.

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, therefore no dose adjustment is necessary.

Long-term combination of ACTASVO 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. A reduction of the dutasteride dosing frequency can be considered if side effects are noted. It should be noted that in the case of enzyme inhibition, the long half-life may be further prolonged, and it can take more than 6 months of concurrent therapy before a new steady state is reached.

Effects of dutasteride on the pharmacokinetics of other medicines

Dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Dutasteride neither inhibits human cytochrome P450 medicine-metabolising enzymes nor induces cytochrome P450 isoenzymes CYP1A, CYP2B and CYP3A.

Dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein, nor do these medicines displace dutasteride. Medicines that have been tested for interactions with dutasteride include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, but no clinically significant interactions have been observed.

No clinically significant adverse interactions have been reported when dutasteride was co-administered with anti-hyperlipidaemics, 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.

No evidence of pharmacokinetic or pharmacodynamic interactions were reported when tamsulosin or terazosin have been administered in combination with dutasteride. The co-administration of dutasteride with tamsulosin showed that the combination with an alpha blocker is well tolerated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

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 dutasteride 0,5 mg daily. 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).

As with all 5 alpha reductase inhibitors, when the patient's partner 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 not known whether dutasteride 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. The possibility of reduced male fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

Most side effects experienced are mild to moderate and occur in the reproductive system.

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Frequency unknown	Allergic reactions including rash, pruritus, urticaria, localised oedema, and angioedema

System Organ Class	Frequency	Adverse reactions
Psychiatric disorders	Frequency unknown	Depression
Skin and subcutaneous tissue disorders	Less frequent	Alopecia (primarily body hair loss), hypertrichosis
Reproductive system and breast disorders	Frequent	Impotence *, altered (decreased) libido*, ejaculation disorders*^ breast disorders+ (4)
	Frequency unknown	Testicular pain and swelling

* These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.

^ includes semen volume decreased.

+ includes breast tenderness and breast enlargement.

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

Results from volunteer studies report that 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 therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given 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. 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 as in ACTASVO 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 dutasteride 0,5 mg, median serum DHT concentrations were reduced by 85 % and 90 % respectively.

In BPH patients treated with dutasteride 0,5 mg 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 oral administration of a single 0,5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours.

The absolute bioavailability in man is approximately 60 %.

The bioavailability of dutasteride is not affected by food.

Distribution

Dutasteride has a large volume of distribution (300 to 500 ℓ) and is highly bound to plasma proteins (> 99,95 %). 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

Dutasteride is extensively metabolised. *In vitro*, dutasteride is metabolised by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite.

In human serum, following dosing to steady state, unchanged dutasteride, three major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasterlde), have been detected.

Elimination

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.

Pharmacokinetics in special patient groups

Elderly

No significant influence of age has been reported on the exposure of dutasteride or the medicine effect as measured by DHT. Therefore, no 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 clinically significant increase of the dutasteride plasma concentrations is anticipated for patients with renal impairment (see section 4.2).

Hepatic impairment

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3). Because dutasteride is eliminated mainly through metabolism the plasma levels of dutasteride are expected to be elevated in these patients and the half-life of dutasteride be prolonged (see section 4.2 and section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Butylhydroxytoluene (E321).

Glycerol monocaprylocaprate Type I

Capsule shell

Gelatin

Glycerol

Lecithin (soya) (E322)

Titanium Dioxide (E171)

Triglycerides

Yellow Iron Oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container to protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ACTASVO soft capsules are packed in heat-sealed Aluminium/PVC-PVDC white opaque blister strips containing 10 capsules per blister. The blister strips are packed in outer cardboard cartons with a leaflet in a pack size of 30 capsules.

6.6 Special precautions for disposal and other handling

Dutasteride 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

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

54/21.12/0010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 April 2025

10. DATE OF REVISION OF THE TEXT