UROKA

(Dutasteride Soft Gelatin Capsules 0.5 mg)

Composition:
Each soft gelatin capsule contains dutasteride 0.5 mg

Description of the Capsule:
Colorless, oily liquid filled in 10 minim, oblong, opaque yellow, soft gelatin capsule.

Pharmacodynamics:
Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors. ATC code: G04C B02.
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 5α-DHT.

Effect on 5 alpha-dihydrotestosterone and testosterone
Effect of daily doses of dutasteride on the reduction on DHT is dose dependant and is observed within 1-2 weeks (85% and 90% reduction, respectively).
In patients with BPH treated with dutasteride 0.5 mg/day, the median decrease in serum 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.

Effect on Prostate Volume
Significant reductions in prostate volume have been detected as early as one month after initiation of treatment and reductions continued through Month 24 ($p<0.001$). Dutasteride led to a mean reduction of total prostate volume of 23.6% (from 54.9 ml at baseline to 42.1 ml) at Month 12 compared with a mean reduction of 0.5% (from 54.0 ml to 53.7 ml) in the placebo group. Significant ($p<0.001$) reductions also occurred in prostate transitional zone volume as early as one month continuing through Month 24, with a mean reduction in prostate transitional zone volume of 17.8% (from 26.8 ml at baseline to 21.4 ml) in the dutasteride group compared to a mean increase of 7.9% (from 26.8ml to 27.5 ml) in the placebo group at Month 12. The reduction of the prostate volume seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Pharmacokinetics:
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 is approximately 60%. 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 0.5mg 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 3.4ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

Biotransformation
In vitro, dutasteride is metabolised by the human cytochrome P450 enzyme CYP450-3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.
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), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known.

Elimination
Dutasteride is extensively metabolized. Following oral dosing dutasteride 0.5mg/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 0.1ng/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 nanograms/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 nanograms/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 to 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).

Indication:
Monotherapy
Dutasteride is indicated for the treatment and control of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.

Combination With Alpha-Blocker
Dutasteride in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

Dosage and Administration:
Adults (including elderly)
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.
Dutasteride may be administered with or without food.
The recommended dose of dutasteride is 1 capsule (0.5 mg) taken orally once daily.
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.
For the treatment of BPH, dutasteride can be administered alone or in combination with the alpha-blocker tamsulosin (0.4mg).

Renal impairment
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of dutasteride is contraindicated.

Contraindications:
Dutasteride is contraindicated in patients with known hypersensitivity to dutasteride, other 5 alpha-reductase inhibitors, or any component of the preparation.
Dutasteride is contraindicated for use in women and children and adolescents.
Dutasteride is contraindicated in patients with severe hepatic impairment.

Warning and Precautions:
General
Lower urinary tract symptoms of BPH can be indicative of urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with dutasteride. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5α-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

Exposure of women and children and adolescents
Dutasteride is absorbed through the skin; therefore, women and children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water. Women who are pregnant or may be pregnant should not handle dutasteride soft gelatin capsules because of the possibility of absorption of dutasteride and the potential risk of a foetal anomaly to a male foetus.

Blood Donation
Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Use in Hepatic Impairment
Dutasteride was not studied in patients with liver disease. Caution should be used in the administration of dutasteride to patients with mild to moderate hepatic impairment.

Combination Therapy with Tamsulosin and Cardiac Failure
No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established. Patients with underlying risk factors for cardiovascular disease, including past or current cardiovascular conditions, advanced age, elevated resting heart rate, should be monitored for signs and symptoms of cardiac failure.

Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in 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.
Dutasteride causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment.
Patients receiving dutasteride should have a new PSA baseline established after 6 months of treatment with dutasteride. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from the lowest PSA level while on dutasteride may signal the presence of prostate cancer (particularly high grade cancer) or non-compliance therapy with dutasteride and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. In the interpretation of PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.
Treatment with dutasteride does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.
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 dutasteride.
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.

Increased Risk of High-Grade Prostate Cancer
5 alpha-reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5 alpha-reductase inhibitors to reduce prostate volume or trial-related factors impacted the results of these trials has not been established.
Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing.

Breast Cancer in Men
Breast cancer has been reported in men taking dutasteride in clinical trials and during the post-marketing period. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. It is not clear if there is a casual relationship between the occurrence of male breast cancer and long term use of dutasteride.

Drug 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 metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 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, acenocoumorol, phenprocoumon, 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 pharmacokinetic or pharmacodynamic 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.

Effects on ability to drive and use machines:
Based on the pharmacodynamic properties of dutasteride, treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

Pregnancy and Lactation:
Fertility: 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.

Common Adverse Effects:
Dutasteride as monotherapy or in combination with tamsulosin:
The most common adverse reactions reported in subjects receiving dutasteride were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders. The most common adverse reactions reported in subjects receiving combination therapy (dutasteride plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness.

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

Immune system disorders
Very rare: Allergic reactions, including rash, pruritus, urticaria, localised oedema and angioedema.

Psychiatric disorders
Very rare: Depressed mood

Skin and subcutaneous tissue disorders
Rare: Alopecia (primarily body hair loss), Hypertrichosis

Reproductive system and breast disorders
Very rare: Testicular pain and testicular swelling

Overdose and treatment:
Single doses of dutasteride up to 40 mg (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.

Pack size/ Presentation:
10's in PVC/PVDC of Alu Blister in carton of 3 blisters.

Shelf Life:
Four years from manufacturing date.

Storage Conditions:
Store below 30°C in a dry place.
Keep out of reach of children.
Jauhi ubat dari kanak-kanak.

Name and Address of Manufacturers:
Packed and released by :
GoodScience Sdn Bhd
No. 7, Jalan KPK 4/3, Kawasan Perindustrian Kundang,
Kundang Jaya, 48020 Rawang, Selangor.

Manufactured by:
MEGA LIFESCIENCES Public Company Limited
384, Moo 4, Soi 6, Bangpoo Industrial Estate,
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