MODULE 1	**:**	**ADMINISTRATIVE INFORMATION & PRODUCT INFORMATION**

1.6 Product Information

1.6.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished Pharmaceutical Product

1.1 Proprietary Name

UROKA CAPSULES

1.2 Strength

EACH SOFT GELATIN CAPSULES CONTAINS DUTASTERIDE 0.5MG.

1.3 Description

COLORLESS, OILY LIQUID, FILLED IN 10MINIM, OBLONG, OPAQUE YELLOW, SOFT GELATIN SHELL CAPSULE.

2. Qualitative and Quantitative composition

2.1 Qualitative Declaration

Recommended International Non-proprietary name (INN):

DUTASTERIDE.

2.2 Quantitative Declaration

Each S0ft gelatin capsule contains: Dutasteride 0.5mg

For full list of Excipients, see section 6.1.

3.0 Pharmaceutical form

SOFT GELATIN CAPSULES.

4.0 Clinical Particulars

4.1 Therapeutic Indications

Monotherapy :

Dutasteride is indicated for the treatment of symptomatic benign prostatic hyperplesia (BPH) in men with an enlarged prostate to:

- Improve symptoms
- Reduce the risk of acute urinary retention (AUR), and as an aid in the detection of prostate cancer.

4.2 Posology and method of administration

The capsule 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 is 1 capsule (0.5mg) taken once daily.

Method of Administration: Oral

4.3 Contraindications

Dutasteride is contraindicated for use in:

- Pregnancy, in animal reproduction and developmental toxicity studies, Dutasteride inhibited development of male fetus external genitalia. Therefore, Dutasteride may cause fetal harm when administered to a pregnant woman. If Dutasteride is used during pregnancy, or if the patient becomes pregnant while taking Dutasteride, the patient should be apprised of the potential hazard to the fetus.
- Women of childbearing potential.
- Pediatric patients.
- Patients with previously demonstrated clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to Dutasteride or other 5 alpha- reductase inhibitors.

4.4 Special Warnings and Precautions for Use

Effects on Prostate-Specific Antigen (PSA) and the use of PSA in Prostate Cancer Detection:

In clinical trials, Dutasteride reduced serum PSA concentration by approximately 50% within 3 to 6 months. This decrease was predictable over the entire range of PSA values in subjects with symptomatic BPH, although it may vary in individuals. Dutasteride may also cause decreases in serum PSA in the presence of prostate cancer. To interpret serial PSAS in men taking Dutasteride, a new PSA baseline should be established at least 3 months after starting treatment and PSA monitored periodically thereafter. Any confirmed increase from the lowest PSA value while on Dutasteride may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the

normal range for men not taking a 5 alpha-reductase inhibitor. Noncompliance with Dutasteride may also affect PSA test results.

To interpret an isolated PSA value in a man treated with Dutasteride for 3 months or more, the PSA value should be doubled for comparison with normal values in untreated men. The free-to-total PSA ratio (percent free 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 receiving Dutasteride, no adjustments to its value appears necessary.

Co-administration of Dutasteride and tamsulosin resulted in similar changes to serum PSA as Dutasteride monotherapy.

Increased risk of High-Grade Prostate Cancer:

In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0ng/mL taking Dutasteride in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8 – 10 prostate cancer compared with men taking placebo (Dutasteride 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5mg, similar results for Gleason score 8 – 10 prostate cancer were observed (finasteride 1.8% versus placebo 1.11%).

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.

valuation for other Urological Diseases:

Prior to initiating treatment with Dutasteride, consideration should be given to other urological conditions that may cause similar symptoms. In addition, BPH and prostate cancer may coexist.

Exposure of Women-Risk to Male Fetus:

Dutasteride capsules should not be handled by a woman who is pregnant or who could become pregnant. Dutasteride is absorbed through the skin and could result in unintended fetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with leaking Dutasteride capsules, the contact area should be washed immediately with soap and water.

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.

Effect on Semen Characteristics:

The effects of Dutasteride 0.5mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n = 23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reductions 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 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%), 2 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 characteristcs for an individual patient's fertility is not known.

Patient Counseling Information

PSA Monitoring:

Physicians should inform patients that Dutasteride reduces serum PSA levels by approximately 50% within 3 to 6 months of therapy, although it may vary for each individual. Afaor patients undergoing PSA screening, increases in PSA levels while on treatment with Dutasteride may signal the presence of prostate cancer and should be evaluated by a healthcare provider.

Increased Risk of High-Grade Prostate Cancer:

Physicians should inform patients that there was an increase in high-grade prostate cancer in men treated with 5 alpha-reductase inhibitors (which are indicated for BPH treatment), including Dutasteride , compared with those treated with placebo in trials looking at the use of these drugs to reduce the risk of prostate cancer.

Exposure of Women-Risk to Male Fetus:

Physicians should inform patients that Dutasteride capsules should not be handled by a woman who is pregnant or who could become pregnant because of the potential for absorption of Dutasteride and the subsequent potential risk to a developing male fetus. Dutasteride is absorbed through the skin and

could result in unintended fetal exposure. If a pregnant woman or woman of childbearing potential comes in contact with leaking Dutasteride capsules, the contact area should be washed immediately with soap and water.

Blood donation:

Physicians should inform men treated with Dutasteride that they should not donate blood until at least 6 months following their last dose to prevent pregnant women from receiving Dutasteride through blood transfusion. Serum levels of Dutasteride are detectable for 4 to 6 months after treatment ends.

4.5 Interaction with other medicinal products and other forms of Interaction Cytochrome P450 inhibitors:

No clinical drug interaction trials have been performed to evaluate the impact of CYP3A enzyme inhibitors on Dutasteride pharmacokinetics. However, based on *in vitro* data, blood concentrations of Dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as Ritonavir, Ketoconazole, Verapamil, Diltiazem, Cimetidine, Troleandomycn and Ciprofloxacin.

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2D6 and CYP3A4) at concentration of 1,000ng/mL, 25 times greater than steady-state serum concentrations in humans.

Alpha Adrenergic Antagonists:

In a single-sequence, crossover trial in healthy volunteers, the administration of tamsulosin or terazosin in combination with Dutasteride had no effect on the steady-state pharmacokinetics of either alpha adrenergic antagonist. Although the effect of administration of tamsulosin or terazosin on Dutasteride pharmacokinetic parameters was not evaluated, the percent change in DHT concentrations was similar for Dutasteride alone compared with the combination treatment.

Calcium Channel Antagonists:

In a population pharmacokinetics analysis, a decrease in clearance of Dutasteride was noted when coadministered with the CYP3A4 inhibitors verapamil (-37%, n=6) and diltiazem (-44%, n=5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was coadministered with Dutasteride with Dutasteride (+7%, n=4).

The decrease in clearance and subsequent increase in exposure to Dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment us recommended.

Cholestyramine:

Administration of a single 5-mg dose of Dutasteride followed 1 hour later by 12g cholestyramine did not affect the relative bioavailability of Dutasteride in 12 normal volunteers.

Digoxin:

In a trial of 20 healthy volunteers, Dutasteride did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5mg/day for 3 weeks.

Warfarin:

In a trial of 23 healthy volunteers,3 weeks of treatment with Dutasteride 0.5mg/day did not alter the steady=state pharmacokinetics of the S-or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

Other Concomitant Therapy:

Although specific interaction trials were not performed with other compounds, approximately 90% of the subjects in the 3 randomized, double-blind, placebo-controlled safety and efficacy trials receiving Dutasteride were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of Dutasteride and concurrent therapy when Dutasteride was coadministered with anti-hyperlipdemics, 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.

4.6 Pregnancy and Lactation

Pregnancy category X:

Dutasteride is contraindicated for use in women of childbearing potential and during pregnancy. It is a 5 alpha-reductase inhibitor that prevents conversion of testosterone to dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, Dutasteride inhibited normal development of external genitalia in male fetuses. Therefore, Dutasteride may cause fetal harm when administered to a pregnant woman.

If Dutasteride is used during pregnancy or if the patient becomes pregnant while taking Dutasteride, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers:

utasteride is contraindicated for use in women of childbearing potential, including nursing women. It is not known whether Dutasteride is excreted in human milk.

Pediatric use:

Dutasteride is contraindicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

From clinical trials with Dutasteride as monotherapy or in combination with tamsulosin:

- The most common adverse reactions 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. Ejaculation disorders occurred significantly more in subjects receiving combination therapy (11%) compared with those receiving Dutasteride (2%) or tamsulosin (4%) as monotherapy.
- Trial withdrawal due to adverse reactions occurred in 4% of subjects receiving Dutasteride and 3% of subjects receiving placebo in placebo-controlled trials with Dutasteride. The most common adverse reaction leading to trial withdrawal was impotence (1%).
- In the clinical trial evaluating the combination therapy, trial withdrawal due to adverse reactions

occurred in 6% of subjects receiving combination therapy (Dutasteride plus tamsulosin) and 4% of subjects receiving Dutasteride or tamsulosin as monotherapy. The most common adverse reaction in all treatment arms leading to trial withdrawal was erectile dysfunction (1% to 1.5%).

4.9 Overdose and treatment

In volunteer trials, single doses of Dutasteride up to 40mg) 80times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical trial, daily doses of 5mg (0 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5mg.

There is no specific antidote for Dutasteride. Therefore, in cases of suspected overdose, symptomatic and supportive treatment should be given as appropriate, taking the long half-life of Dutasteride into consideration.

5 Pharmacological properties

5.3 Pharmacodynamic Properties

Effect on 5 alpha-dihydrotestosterone and testosterone:

The effect of Dutasteride on reduction of DHT is dose dependent. The maximum effect is observed within 1 to 2 weeks and median serum DHT concentrations decreased by 85% and 90% at 1 and 2 weeks after initiation of daily 0.5mg Dutasteride, respectively. In patients with BPH treated with Dutasteride 0.5mg/day for 4 years. The median decrease in serum testosterone was 19% at both 1 and 2 years, 26% at 3 years and 22% at 4 years, but the mean and median levels remained within the physiologic range.

In patients with BPH treated with 5mg/day of Dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the Dutasteride group compared with placebo (784 and 5,793 pg/g, respectively, $P < 0.001$). Mean prostatic tissue concentrations of testosterone were significantly higher in the Dutasteride group compared with placebo (2,073 and 93 pg/g, respectively, $P < 0.001$).

Adult mails with genetically inherited type 2 5 aipha-reductase deficiency also have decreased DHT levels. These 5 aipha-reductase deficient males have a small prostate gland throughout life and do not develop BPH except for associated urogenital defects present at birth, no other clinical abnormalities related to 5 alpha-reductase deficiency have been observed in these individuals.

Effects on other hormones:

In healthy volunteers, 52 weeks of treatment with Dutasteride 0.5 mg/day (n = 26) resulted in no clinically significant change compared with placebo (n = 23) in sex hormone-binding globulin, estradiol. Luteinizing hormone, follicle – stimulating hormone, thyroxine (free T4) and dehydroepiandrosterone. Statistically significant , baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1ng/dL, $P < 0.003$) and thyroid-stimulating hormone at 52 weeks (0.4 microunits/mL, $P < 0.05$). The median percentage changes from baseline within the Dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid-stimulating hormone at 52 weeks. After stopping Dutasteride for 24 weeks, the mean levels of testosterone and thyroid-stimulating hormone had returned o baseline in the group of subjects with available data at the visit. In subjects with BPH treated with Dutasteride in large randomized, double-blind, placebo-controlled trial, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at both 12 and 24 months.

Other effects:

Plasma lipid panel and bone mineral density were evaluated following 52 weeks of Dutasteride 0.5mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-rayabsorptiometry compared with eighther placebo or baseline. In addition, the plasma lipid profile (i.e. total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) was unaffected by Dutasteride. No clinically significant changes in adrenal hormone responses to adrenocorticotropic hormone (ACTH) stimulation were observed in a subset population (n = 13) of the 1-year volunteer trial.

5.4 Pharmacokinetic Properties

Absorption

Following administration of a single 0.5mg dose of a soft gelatin capsule, time to peak serum concentrations (T_{max}) of Dutasteride occurs within 2 to 3 hours. Absolute bioavailability in 5 ubjects is approximately 60% (range: 40% to 94%). When drug is administered with food, the maximum serum concentrations were reduced by 10% to 15%. This reduction is no clinical significance.

Distribution:

Based on pharmacokinetiucs profiles of single and repeated doses, Dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6).

In a trial of healthy subjects, (n = 26) receiving Dutasteride 0.5mg/day for 12 months, semen Dutasteride concentrations averaged 3.4ng/mL (range:L 0.4 to 14 ng/mL) at 12 months and similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months 11.5% of serum Dutasteride concentrations partitioned into semen.

Metabolism and elimination:

Dutasteride is extensively metabolized in humans. In vitro studies showed that Dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride and the 6, 4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. 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. In vitro, the 4'-hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much less potent than Dutasteride against both isoforms of human 5 alpha-reductase. The activity of 6β-hydroxydutasteride is comparable to that of Dutasteride.

Dutasteride and its metabolites were excreted mainly in feces. As a percentage of dose, there was approximately 5% unchanged Dutasteride (~1% to ~15%) and 40% as Dutasteride - related metabolites (~2% to ~90%). Only trace amounts of unchanged Dutasteride were found in urine (< 1%). Therefore, on average, he dose unaccounted for approximated 55% (range: 5% to 97%).

The terminal elimination half-life of Dutasteride is approximately 5 weeks at steady state. The average steady-state serum Dutasteride is concentration was 40 ng/mL following 0.5mg/day for 1 year. Following daily dosing, Dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of

Dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL for up to 4 to 6 months after discontinuation of treatment.

Pharmacokinetics in Specific Populations:

Pediatric:

Dutasteride pharmacokinetics have not been investigated in subjects younger than 18 years.

Geriatric:

No dose adjustment is necessary in the elderly.

Gender:

Dutasteride indicated in pregnancy and women of childbearing potential and is not indicated for use in other women. The pharmacokinetics of Dutasteride in women have not been studied.

Race:

The effect of race on Dutasteride pharmacokinetics has not been studied.

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 of hepatic impairment on Dutasteride pharmacokinetics has not been studied. Because Dutasteride is extensively metabolized, exposure could be higher in hepatic impaired patients.

5.5 Preclinical Safety Data

Not applicable.

6 Pharmaceutical Particulars

6.1 List of Excipients:

Inactive ingredients:
Mono-and Di-glycerides (Capmul MCM NF)
Butylhydroxytoluene
Capsule shell ingredients:
Gelatin
Glycerine
Iron oxide yellow
Titanium dioxide
Purified water

6.2 Incompatibilities

None.

6.3 Shelf Life

48 months

6.4 Special Precautions for Storage

Store below 30°C in a dry place.

6.5 Nature and Contents of Container

Blisters 10 capsules, 3 blisters packed in an in a printed unit carton with a literature insert.

6.6 Special precaution for disposal and other handling

No special requirements.

MODULE 1	**:**	**ADMINISTRATIVE INFORMATION & PRODUCT INFORMATION**

7 Marketing Authorization Holder and Manufacturing Site Addresses

Marketing Authorization Holder:

MEGA LIFESCIENCES Public Company Limited

384 Moo 4, Soi 6, Bangpoo Industrial Estate, Pattana 3 Road, Phraeksa, Mueang, Samutprakarn 10280, Thailand.

Manufacturing Site Address:

MEGA LIFESCIENCES Public Company Limited

384 Moo 4, Soi 6, Bangpoo Industrial Estate, Pattana 3 Road, Phraeksa, Mueang, Samutprakarn 10280, Thailand.

8 Marketing Authorization Number

9 Date of first Registration/ Renewal of the Registration

10 Date of revision of the text