1. **Name of the Medicinal Product :**
   1.1 **Product Name :** UROKA PLUS (Dutasteride 0.5mg and Tamsulosin Hydrochloride 0.4mg hard capsules)
   1.2 **Strength :** Dutasteride 0.5mg and Tamsulosin HCl 0.4mg
   1.3 **Pharmaceutical Dosage Form :** Hard capsule

2. **Quality and Quantitative Composition :**
   2.1 Qualitative Declaration
   INN Name: Dutasteride
   IUPAC Name: (5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide

   INN Name: Tamsulosin Hydrochloride
   IUPAC Name: (-)-(R)-5-[2-[[2-(o-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy benzenesulfonamide, monohydrochloride

Ingredients	Reference
DUTASTERIDE 0.5MG SOFT CAPSULES	
Active:	
Dutasteride	Ph.Eur & Mfg Specs
Excipients of capsule content:	
Glycerol monocaprylocaprate type I	Ph.Eur
Butylhydroxytoluene (BHT) - (E-321)	Ph.Eur
Excipients of capsule shell:	
Gelatin	Ph.Eur
Glycerol	Ph.Eur
Purified water	Ph.Eur
Titanium Dioxide (E-171)	Ph.Eur
Yellow Iron Oxide (E-172)	
Triglycerides, medium chain	Ph.Eur
Lecithin (soya) (E-322)	USP
TAMSULOSIN HCL 0.4MG PELLETS	
Active:	
Tamsulosin Hydrochloride	Ph.Eur
Excipients:	
Microcrystalline cellulose	Ph.Eur
Magnesium stearate	Ph.Eur
Methacrylic acid – Ethyl acrylate coloymer (1:1) Dispersion (30%)	Ph.Eur
Purified water	Ph.Eur
Enteric coat:	

Methacrylic acid –Ethyl acrylate copolymer (1:1)	Ph.Eur
Sodium Hydroxide	Ph.Eur
Triacetin	USP
Purified Talc	Ph.Eur
Titanium Dioxide (E-171)	Ph.Eur
Purified water	Ph.Eur
Extragranular:	
Talc	Ph.Eur
HARD CAPSULES	
Actives:	
Dutasteride	Ph.Eur & Mfg Specs
Tamsulosin HCl 0.4mg pellets	Ph.Eur
Capsule Cap:	
Hypromellose - Substitution type 2208 (4 mPa.s & 3 mPa.s) - Substitution type 2910 (6 mPa.s & 4.5 mPa.s)	Ph.Eur
Potassium Chloride	Ph.Eur
Carrageenan	Ph.Eur
Titanium Dioxide (E-171)	Ph.Eur
Sunset Yellow (E-110)	EC Directive 2009/35 & 231/2012
Water *	Ph.Eur
Capsule Body:	
Potassium Chloride	Ph.Eur
Carrageenan	Ph.Eur
Titanium Dioxide (E-171)	Ph.Eur
Hypromellose - Substitution type 2208 (4 mPa.s & 3 mPa.s) - Substitution type 2910 (6 mPa.s & 4.5 mPa.s)	Ph.Eur
Red Iron Oxide (E-172)	Meets specification described in the regulation 231/2012/EU and subsequent and related amendments and updates, laying down specifications for food additives
Purified water	Ph.Eur

2.2 Quantitative Declaration

a) Dutasteride 0.5mg soft capsules

Ingredients	Reference*	Dosage (mg) / capsule	Function
Active substance			
Dutasteride	Ph.Eur[1] & Mfg Specs[3]	0.5	Drug Substance
Excipients of capsule content			
Glycerol monocaprylocaprate type I	Ph.Eur[1]	199.5	Solvent / Carrier
Butylhydroxytoluene (BHT) - (E-321)	Ph.Eur[1]	0.02	Antioxidant
Total capsule content weight		***200.02mg***	
Excipients of capsule shell			
Gelatin	Ph.Eur[1]	112.5	Capsule shell former
Glycerol	Ph.Eur[1]	64.2	Plasticizer
Purified water[2]	Ph.Eur[1]	88.3	Solvent
Total gelatin mass weight		***265.0mg***	
Titanium Dioxide (E-171)	Ph.Eur[1]	1.214	Opacifier
Yellow Iron Oxide (E-172)[4]		0.100	Colourant
Triglycerides, medium chain[5]	Ph.Eur[1]	q.s.	Lubricant
Lecithin (soya) (E-322)[5]	USP[1]	q.s.	Lubricant
Total capsule shell weight		***266.3mg***	
Total capsule weight		**466.3mg**	

(1) Current edition is applied
(2) It is partially evaporated during the manufacturing process
(3) Mfg. Specs: Manufacturer Specifications
(4) Complies with purity standards set out in Regulation (EU) No 231/2012 of the Commision, on
March 9th, 2012, 94/36/CE and 2008/128/CE
(5) Used during the capsulation process for the lubrication of the gelatin layers

b) Tamsulosin HCl 0.4mg pellets

Ingredients	Reference*	Dosage (mg) / capsule	Function
Active substance			
Tamsulosin Hydrochloride*	Ph.Eur[1]	0.4	Drug Substance
Excipients			
Microcrystalline cellulose	Ph.Eur[1]	194.4	Diluent
Magnesium stearate	Ph.Eur[1]	5.7	Rate controlling agent
Methacrylic acid – Ethyl acrylate coloymer (1:1) Dispersion (30%)	Ph.Eur[1]	75.0	Release controlling polymer
Purified water[2]	Ph.Eur[1]	q.s.	Solvent
Theoretical weight of uncoated pellets		***275.5mg***	
Enteric coat			
Methacrylic acid –Ethyl acrylate copolymer (1:1)	Ph.Eur[1]	6.888	Enteric polymer
Sodium Hydroxide	Ph.Eur[1]	0.088	Alkalizing agent
Triacetin	USP[1]	1.035	Plasticizer
Purified Talc	Ph.Eur[1]	1.368	Antitacking agent
Titanium Dioxide (E-171)	Ph.Eur[1]	0.117	Opacifier
Purified water[2]	Ph.Eur[1]	q.s.	Solvent
Theoretical weight of coated pellets		***285.0mg***	
Extragranular Talc	Ph.Eur[1]	0.280	Lubricant
TOTAL		**285.28 mg**	

(1) Current edition is applied
(2) It is partially evaporated during the manufacturing process
*0.40mg of Tamsulosin hydrochloride is equivalent to 0.367mg of Tamsulosin.

Hard capsules

Ingredients	Reference*	Dosage/ capsule	Function
Active intermediate products			
Dutasteride	Ph.Eur[1] & Mfg Specs[3]	1 capsule	Active intermediate product
Tamsulosin HCl 0.4mg pellets	Ph.Eur[1]	285.28 mg	Active intermediate product
Excipients			
Capsule cap			
Hypromellose - Substitution type 2208 (4 mPa.s & 3 mPa.s) - Substitution type 2910 (6 mPa.s & 4.5 mPa.s)	Ph.Eur[1]	40.3 mg	Adhesive
Potassium Chloride	Ph.Eur[1]	0.20 mg	Gelling agent
Carrageenan	Ph.Eur[1]	0.37 mg	Viscosity increasing agent
Titanium Dioxide (E-171)	Ph.Eur[1]	2.76 mg	Opacifier
Sunset Yellow (E-110)	EC Directive 2009/35 & 231/2012	0.06 mg	Colourant
Water *	Ph.Eur[1]	2.3 mg	Solvent
Total weight Gelatin Capsule Cap		***46.00 mg***	
Capsule body			
Potassium Chloride	Ph.Eur[1]	0.31 mg	Gelling agent
Carrageenan	Ph.Eur[1]	0.55 mg	Viscosity increasing agent
Titanium Dioxide (E-171)	Ph.Eur[1]	0.69	Opacifier
Hyprmellose - Substitution type 2208 (4 mPa.s & 3 mPa.s) - Substitution type 2910 (6 mPa.s & 4.5 mPa.s)	Ph.Eur[1]	60.55 mg	Adhesive
Red Iron Oxide (E-172)	Meets specification described in the regulation 231/2012/EU and subsequent and	3.45 mg	Colourant

	related amendments and updates, laying down specifications for food additives		
Water Purified*	Ph.Eur[1]	q.s.	Solvent
Total weight capsule body		***69.0mg***	
Total empty capsule		***115.0 mg***	
TOTAL CAPSULE[2]		**866.58 mg**	

(1) Current Edition
(2) The total weight could have a deviation due to the variability of the soft gelatin weight and the
gelatin empty capsule weight.
* Target moisture

3. **Pharmaceutical form:** Uroka Plus is presented as hard capsules with brown body and orange cap. The hard capsules contain: one Dutasteride 0.5 mg soft gelatin capsule and Tamsulosin HCl pellets in the equivalent weight of 0.4 mg of Tamsulosin HCl.

4. Clinical Particulars:

4.1 Therapeutic indications:

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

4.2 Posology and method of administration:

Adults (including elderly)
The recommended dose of Uroka Plus is one capsule (0.5 mg/ 0.4mg) once daily.

Where appropriate, Uroka Plus may be used to substitute concomitant Dutasteride and Tamsulosin hydrochloride in existing dual therapy to simplify treatment.

Where clinically appropriate, direct change from Dutasteride or Tamsulosin hydrochloride monotherapy to Uroka Plus may be considered.

Renal impairment

The effect of renal impairment on dutasteride-tamsulosin 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-tamsulosin 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 Uroka Plus is contraindicated.

Paediatric population
Uroka Plus is contraindicated in the paediatric population (under 18 years of age).

Method of administration

For oral use.

Patients should be instructed to swallow the capsules whole, approximately 30 minutes after the same meal each day. The capsules should not be chewed or opened. Contact with the contents of the Dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Contraindications :
Uroka Plus is contraindicated in:

- women and children and adolescents
- patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin (including tamsulosin-induced angio-edema), soya, peanut or any of the other excipients listed.
- patients with a history of orthostatic hypotension.
- patients with severe hepatic impairment.

4.3 Special warning and precautions for use :
Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events (including cardiac failure) and after consideration of alternative treatment options including monotherapies.

Prostate cancer and high grade tumours
The REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled study investigated the effect of dutasteride 0.5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2.5 to 10 ng/ml and a negative prostate biopsy 6 months before study enrolment) compared to placebo. Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (n=29, 0.9%) compared to placebo (n=19, 0.6%). The relationship between dutasteride and Gleason 8 - 10 prostate

cancers is not clear. Thus, men taking Uroka Plus should be regularly evaluated for prostate cancer.

Prostate specific antigen (PSA)

Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Uroka Plus causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment.

Patients receiving Uroka Plus should have a new PSA baseline established after 6 months of treatment with Uroka Plus. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on Uroka Plus may signal the presence of prostate cancer or noncompliance to therapy with Uroka Plus and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-alpha reductase inhibitor. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with Uroka Plus 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 Uroka Plus. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Uroka Plus therapy, no adjustment to its value appears necessary.

Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with Uroka Plus and periodically thereafter.

Cardiovascular adverse events

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 dutasteride and an alpha1- adrenoceptor antagonist, 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 alpha1-adrenoceptor antagonists do not support a conclusion on increased cardiovascular risks.

Breast neoplasia

There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-alpha reductase inhibitors. Physicians should instruct their

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

Renal impairment
The treatment of patients with severe renal impairment (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Hypotension
Orthostatic: As with other alpha1- adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with Uroka Plus should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved.

In order to minimise the potential for developing postural hypotension the patient should be haemodynamically stable on an alpha1- adrenoceptor antagonist prior to initiating use of PDE5 inhibitors.

Symptomatic: Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil). Alpha1- adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with Uroka Plus in patients for whom cataract surgery is scheduled is therefore not recommended.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with Uroka Plus in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established.

Leaking capsules
Dutasteride is absorbed through the skin, therefore, women, 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.

Inhibitors of CYP3A4 and CYP2D6

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 (e.g. ketoconazole), or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin exposure. Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Hepatic impairment

Uroka Plus has not been studied in patients with liver disease. Caution should be used in the administration of Uroka Plus to patients with mild to moderate hepatic impairment.

Excipients

This medicinal product contains the colouring agent Orange Yellow S (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of Interactions:

There have been no drug interaction studies for Uroka Plus. The following statements reflect the information available on the individual components.

Dutasteride

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection.

Effects of other drugs on the pharmacokinetics of dutasteride

Dutasteride is mainly eliminated via metabolism. *In vitro* studies indicate that this metabolism is catalysed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1.6 to 1.8 times greater, respectively, in a small number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P-glycoprotein) than in other patients.

Long-term combination of dutasteride with drugs that are potent inhibitors of the enzyme CYP3A4 (e.g. ritonavir, indinavir, nefazodone, itraconazole, ketoconazole administered orally) may increase serum concentrations of dutasteride. Further inhibition of 5-alpha reductase at increased dutasteride exposure, is not likely. However, 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.

Administration of 12 g cholestyramine one hour after a 5 mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other drugs
In a small study (n=24) of two weeks duration in healthy men, dutasteride (0.5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamic interaction in this study.

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P-glycoprotein.

In vitro interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

Tamsulosin
Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha1- adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride/Tamsulosin should not be used in combination with other alpha1-adrenoceptor antagonists.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure.

Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride- tamsulosin is used in combination with cimetidine.

A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited in vitro and *in vivo* studies are inconclusive. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant furosemide brings about a fall in plasma levels of tamsulosin, but as levels remain within the normal range posology need not be adjusted.

In vitro neither diazepam nor propranolol, trichlormethiazide, chlormadinon, amitryptyline, diclofenac, glibenclamide and simvastatin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide, and chlormadinon.

4.6 Pregnancy and lactation:

Uroka Plus is contraindicated for use by women. There have been no studies to investigate the effect of Uroka Plus on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components.

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 fetus, inhibit the development of the external genitalia of the foetus. Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. It is not known whether a male foetus will 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.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits showed no evidence of foetal harm.

Breast-feeding

It is not known whether dutasteride or tamsulosin are 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.

Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

4.7 Effects on ability to drive and use machine:

No studies on the effects of Uroka Plus on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Uroka Plus.

4.8 Adverse reactions :

The data presented here relate to the co-administration of dutasteride and tamsulosin from the 4 year analysis of the CombAT study, a comparison of dutasteride 0.5mg and tamsulosin 0.4mg once daily for four years as co- administration or as monotherapy. Bioequivalence of Uroka Plus with co-administered dutasteride and tamsulosin has been demonstrated. Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided. Note that not all the adverse events reported with the individual components have been reported with Uroka Plus and these are included for information for the prescriber.

Data from the 4 year CombAT study have shown that the incidence of any investigator- judged drug-related adverse event during the first, second, third and fourth years of treatment respectively was 22%, 6%, 4% and 2% for dutasteride + tamsulosin co-administration therapy, 15%, 6%, 3% and 2% for dutasteride monotherapy and 13%, 5%, 2% and 2% for tamsulosin monotherapy. The higher incidence of adverse events in the co-administration therapy group in the first year of treatment was due to a higher incidence of reproductive disorders, specifically ejaculation disorders, observed in this group.

The investigator-judged drug-related adverse events have been reported with an incidence of greater than or equal to 1% during the first year of treatment in the CombAT Study, BPH monotherapy clinical studies and REDUCE study are shown in the table below.

In addition the undesirable effects for tamsulosin below are based on information available in the public domain. The frequencies of adverse events may increase when the combination therapy is used.

The frequency of adverse reactions identified from clinical trials:

Common; ≥1/100 to <1/10, Uncommon; ≥1/1000 to <1/100, Rare; ≥1/10,000 to <1/1000, Very rare; <1/10,000. Within each SOC grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Reaction	Dutasteride + Tamsulosin[a]	Dutasteride	Tamsulosin[c]
Nervous System Disorders	Syncope	-	-	Rare
	Dizziness	Common	-	Common
	Headache	-	-	Uncommon
Cardiac Disorders	Cardiac Failure (Composite term[1])	Uncommon	Uncommon[d]	-
	Palpitations	-	-	Uncommon

Vascular Disorders	Orthostatic Hypotension	-	-	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Rhinitis	-	-	Uncommon
Gastrointestinal Disorders	Constipation	-	-	Uncommon
	Diarrhoea	-	-	Uncommon
	Nausea	-	-	Uncommon
	Vomiting	-	-	Uncommon
Skin and Subcutaneous Disorders	Angioedema	-	-	Rare
	Stevens-Johnson Syndrome	-	-	Very Rare
	Urticaria	-	-	Uncommon
	Rash	-	-	Uncommon
	Pruritus	-	-	Uncommon
Reproductive System and Breast Disorders	Priapism	-	-	Very Rare
	Impotence[3]	Common	Common[b]	-
	Altered (decreased) libido[3]	Common	Common[b]	-
	Ejaculation disorders[3]^	Common	Common[b]	Common
	Breast Disorders[2]	Common	Common[b]	-
General Disorders and Administration Site Disorders	Asthenia	-	-	Uncommon

[a] Dutasteride + tamsulosin: from CombAT study - the frequencies of these adverse events decrease over time of treatment, from year 1 to year 4.
[b] Dutasteride: from BPH monotherapy clinical studies.
[c] Tamsulosin: from EU Core Safety Profile for tamsulosin.
[d] REDUCE study
[1] Cardiac failure composite term comprised of cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left

ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.
[2] Includes breast tenderness and breast enlargement.
[3] 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 not known.
[^] Includes semen volume decreased.

Other data-

The REDUCE study revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo. Whether the effect of dutasteride to reduce prostate volume, or study related factors, impacted the results of this study has not been established.

The following has been reported in clinical trials and post-marketing use: male breast cancer.

Post marketing Data

Adverse events from world-wide post-marketing experience are identified from spontaneous post-marketing reports; therefore the true incidence is not known.

Dutasteride
Immune system disorders

Not known: Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.

Psychiatric disorders Not known:
Depression

Skin and subcutaneous tissue disorders

Uncommon: Alopecia (primarily body hair loss), hypertrichosis.

Reproductive system and breast disorders

Not known: Testicular pain and testicular swelling

Tamsulosin
During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha1- adrenoceptor antagonists, including tamsulosin.

In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, ejaculation failure and dry mouth have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

4.9 Overdose and special antidotes :

No data are available with regard to overdosage of Uroka Plus. The following statements reflect the information available on the individual components.

Dutasteride

In volunteer studies, single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects 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 suspected overdosage symptomatic and supportive treatment should be given as appropriate.

Tamsulosin

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed which were treated with fluid replacement and the patient could be discharged the same day. In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders, and when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52

Mechanism of action

Dutasteride-tamsulosin is a combination of two drugs: dutasteride, a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α_{1a} and α_{1d} adrenoreceptors. These drugs have complementary mechanisms of action that rapidly

improve symptoms, urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

Dutasteride inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for prostate growth and BPH development. Tamsulosin inhibits α_{1a} and α_{1d} adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α_1-receptors in the prostate are of the α_{1a} subtype.

Tamsulosin

Tamsulosin increases maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in the prostate and urethra, thereby improving voiding symptoms. It also improves the storage symptoms in which bladder instability plays an important role. These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterization is significantly delayed.

A1-adrenoreceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

5.2 Pharmacokinetic Properties:

Absorption

Dutasteride: 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.

Tamsulosin: Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Both the rate and extent of absorption of tamsulosin are reduced when taken within 30 minutes of a meal. Uniformity of absorption can be promoted by the patient always taking Uroka Plus after the same meal. Tamsulosin shows dose proportional plasma exposure.

After a single dose of tamsulosin in the fed state, plasma concentrations of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, the mean steady state Cmax in patients is about two thirds higher than that reached after a single dose. Although this was observed in elderly patients, the same finding would also be expected in younger patients.

Distribution

Dutasteride: Dutasteride has a large volume of distribution (300 to 500 L) and 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 0.5 mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Tamsulosin: In man tamsulosin is about 99% bound to plasma proteins. The volume of distribution is small (about 0.2l/kg).

Biotransformation

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

Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged 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.

Tamsulosin: There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolised by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolising enzymes may lead to increased exposure to tamsulosin. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Elimination

Dutasteride: The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable. 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 therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

Tamsulosin: Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged active substance.

Following intravenous or oral administration of an immediate-release formulation, the elimination half life of tamsulosin in plasma range from 5 to 7 hours. Due to the absorption rate-controlled pharmacokinetics with tamsulosin modified release capsules, the apparent elimination half life of tamsulosin in the fed state is approximately 10 hours and in the steady state in patients approximately 13 hours.

Elderly

Dutasteride: Dutasteride pharmacokinetics 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. No significant influence of age was seen on the exposure of dutasteride but the half-life was shorter in men under 50 years of age. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old.

Tamsulosin: Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in elderly males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal impairment

Dutasteride: 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.

Tamsulosin: The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CL_{cr} < 70$ mL/min/1.73m^2) or moderate-severe ($10 \leq CL_{cr} < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects ($CL_{cr} > 90$ mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with endstage renal disease ($CL_{cr} < 10$ mL/min/1.73m^2) have not been studied.

Hepatic impairment

Dutasteride: The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied. 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.

Tamsulosin: The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

5.3 Preclinical safety Data:

Non-clinical studies have not been conducted with Uroka Plus. Dutasteride and tamsulosin hydrochloride individually have been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5 alpha-reductase inhibitors and alpha1- adrenoceptor antagonists. The following statements reflect the information available on the individual components.

Dutasteride

Current studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans.

Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride). The clinical relevance of these findings is unknown.

As with other 5 alpha reductase inhibitors, feminisation of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminisation of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

Tamsulosin

Studies of general toxicity and genotoxicity did not show any particular risk to humans other than those related to the pharmacological properties of tamsulosin.

In carcinogenicity studies in rats and mice, tamsulosin hydrochloride produced an increased incidence of proliferative changes of the mammary glands in females. These findings, which are probably mediated by hyperprolactinaemia and only occurred at high dose levels, are regarded as not clinically relevant.

High doses of tamsulosin hydrochloride resulted in a reversible reduction in fertility in male rats considered possibly due to changes of semen content or impairment of

ejaculation. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of fetal harm.

6. Pharmaceutical Particulars:

6.1 List of excipients:

Hard Capsule Shell: Hypromellose, Potassium Chloride, Carrageenan, Titanium Dioxide (E171), Iron Oxide Red (E172), Sunset Yellow (E110).

Contents in Dutasteride Soft Capsule:

Content in the Capsule: Glycerol monocaprylocaprate, Butylhydroxytoluene (E321)
Soft Capsule Shell: Gelatin, Glycerol, Titanium Dioxide (E171), Iron Oxide Yellow (E172), Triglycerides medium chain, Lecithin (soya) (E322)

Tamsulosin pellets: Microcrystalline cellulose, Methacrylic acid-ethyl acrylate copolymer 1:1 dispersion 30%, Magnesium stearate, Sodium hydroxide, Triacetin, Talc, Titanium Dioxide (E171)

6.2 Incompatibilities: Not applicable

6.3 Shelf life: 3 years

6.4 Special precautions for storage:

Keep out of reach of children
Protect from light and moisture
Store below 30°C in a dry place

6.5 Nature and contents of container:

Uroka Plus is available as alu-alu blister pack of 6 capsules. Such 5 blisters are packed in a carton.

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

7. Marketing Authorization Holder and manufacturing site address:

Marketing Authorization Holder:
Mega Lifesciences Public Company Limited
384 Moo 4, Pattana 3 Road,
Bangpoo Industrial Estate,
Soi 6, Preaksa, Muang Samutprakarn,
Samutprakarn 10280, Thailand

Manufacturing site address:
SAG MANUFACTURING, S.L.U.
Carretera Nacional I, Km. 36
28750 San Agustin de Guadalix (Madrid)
Spain

8. Marketing Authorization Number: --

9. Date of first authorization / renewal of the authorization : --

10. Date of revision of the text: --