

# NUVANIV™

## Dutasteride

### QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral use contains 0.5 mg dutasteride (*see List of Excipients*).

### PHARMACEUTICAL FORM

Soft capsules: salmon (pink), opaque, oblong, soft gelatin capsules imprinted with 'GS MUF'.

### CLINICAL PARTICULARS

#### Indications

*NUVANIV* is indicated for the treatment of male pattern hair loss (androgenetic alopecia) (*see Clinical Studies*).

#### Dosage and Administration

Capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa.

*NUVANIV* may be taken with or without food (*see Pharmacokinetics*).

The recommended dose of *NUVANIV* is one capsule (0.5 mg) taken orally once a day.

An improvement may be observed after 12 weeks of therapy. Patients may need to be treated for at least six months in order to assess objectively whether a satisfactory response to the treatment can be achieved.

#### 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 Pharmacokinetics – Renal impairment*).

#### Hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (*see Warnings and Precautions and Pharmacokinetics*). In patients with severe hepatic impairment, the use of dutasteride is contraindicated (see section *Contraindications*).

## Contraindications

*NUVANIV* is contraindicated in patients with known hypersensitivity to dutasteride, other 5 alpha-reductase inhibitors, or any component of the preparation (*see List of Excipients*).

*NUVANIV* is contraindicated for use in women and children (*see Pregnancy and Lactation*).

*NUVANIV* is contraindicated in patients with severe hepatic impairment.

## Warnings and Precautions

*NUVANIV* has been studied in clinical trials for treatment of androgenetic alopecia in subjects 18-50 years old (*see Clinical Studies*). Efficacy data for subjects over 50 years old is not available.

### Prostate cancer

In a 4-year study of over 8,000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), 1,517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8 to 10 prostate cancers in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between dutasteride and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing.

In an additional 2-year follow-up study with the original patients from the dutasteride chemoprevention study (REDUCE), a low rate of new prostate cancers were diagnosed (dutasteride [n=14, 1.2%] and placebo [n=7, 0.7%]), with no new identified cases of Gleason 8–10 prostate cancers.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1.02, 95% CI 0.97-1.08) or survival after prostate cancer diagnoses (HR 1.01, 95% CI 0.85-1.20).

### Prostate specific antigen (PSA)

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. Generally, a total serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy.

Physicians should be made aware that a baseline PSA less than 4 ng/ml in patients taking dutasteride does not exclude a diagnosis of prostate cancer. Dutasteride causes a decrease

in mean serum PSA levels by approximately 50% after six months of treatment. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL).

Patients receiving dutasteride who are eligible for prostate cancer screening 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 lowest PSA level while on dutasteride may signal the presence of prostate cancer or non-compliance to therapy with dutasteride and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI. In the interpretation of a 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.

Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients prior to initiating therapy with dutasteride 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 higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low ( $\leq 1\%$ ) and variable between the studies. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (*see Clinical Studies*).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of dutasteride (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

### **Breast cancer in men**

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-ARIs (see *Clinical Studies*). Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

### **Leaking capsules**

Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water (see *Pregnancy and Lactation*).

### **Hepatic impairment**

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of three to five weeks, caution should be used in the administration of dutasteride to patients with liver disease (see *Dosage and Administration and Pharmacokinetics*).

### **Interactions**

*In vitro* drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4 and CYP3A5. Therefore blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 and CYP3A5.

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. Long term combination of dutasteride with drugs that are potent inhibitors of the enzyme CYP3A4 (e.g. ritonavir, indinavir, nefazodone, itraconazol, 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.

*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, acenocoumrol, phenprocoumon diazepam, 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 for Benign Prostatic Hyperplasia (BPH) 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.

## **Pregnancy and Lactation**

### **Fertility**

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post treatment follow-up. At 52 weeks, the mean percent reduction 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 placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count 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%), two 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 possibility of reduced male fertility cannot be excluded.

### **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 (*see Non-Clinical Information*).

### **Lactation**

It is not known whether dutasteride is excreted in breast milk.

## **Effects on Ability to Drive and Use Machines**

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

## **Adverse Reactions**

### **Clinical Trial Data**

Data is presented below from clinical studies of dutasteride in Alopecia and Benign Prostatic Hyperplasia patients.

### **Data from Alopecia patients**

*NUVANIV* has been studied for the treatment of androgenetic alopecia in three six-month clinical studies: Study ALO106377 (a randomised, double-blind, placebo-controlled study to assess the efficacy and safety of dutasteride 0.5mg once daily), Study ARIA2004 (a randomised, double-blind, placebo-controlled, dose-ranging study of dutasteride and finasteride), and Study ARI114263 (a randomised, double-blind, placebo-controlled study to assess the efficacy and safety of dutasteride 0.5 mg, 0.1 mg, 0.02 mg, finasteride 1 mg, or placebo).

In the alopecia studies ALO106377, ARIA2004, and ARI114263, the following investigator-judged drug-related adverse events ( $\geq 2\%$ ) have been reported more commonly on *NUVANIV* treatment compared to placebo:

<b>Number of Subjects with Drug-related Adverse Events (<math>\geq 2\%</math>) Occurring more Frequently in <i>NUVANIV</i> Groups Compared to Placebo.</b>				
<b>Study</b>	<b>Drug-Related AE</b>	<b>Placebo</b>	<b>Dut</b>	
			<b>0.1mg</b>	<b>0.5mg</b>
ARIA2004		N=64	N=72	N=68
	Ejaculation disorders	0	3 (4%)	1 (1%)
	Headaches	2 (3%)	6 (8%)	4 (6%)
	Gastrointestinal discomfort & pain	0	1 (1%)	2 (3%)
ARI114263		N=181	N=188	N=184
	Erectile dysfunction	6 (3%)	6 (3%)	10 (5%)
	Libido decreased	2 (1%)	9 (5%)	4 (2%)
	Abdominal pain	2 (1%)	4 (2%)	0
	Ejaculation disorder	1(<1%)	3(2%)	2(1%)
ALO106377		N=75	-	N=73
	Sexual dysfunction	2 (3%)	-	3 (4%)

#### **Data from Benign Prostatic Hyperplasia (BPH) patients**

The following investigator-judged drug-related adverse events (with incidence more than or equal to 1%) have been reported more commonly in the three phase III placebo controlled studies on dutasteride treatment compared to placebo:

Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
	<i>Placebo</i> (n= 2158)	<i>Dutasteride</i> (n=2167)	<i>Placebo</i> (n=1736)	<i>Dutasteride</i> (n= 1744)
Impotence*	3%	6%	1%	2%
Altered (decreased) libido*	2%	4%	<1%	<1%
Ejaculation disorders*	<1%	2%	<1%	<1%
Breast disorders +	<1%	1%	<1%	1%

\* 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 breast tenderness and breast enlargement

No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

### **Postmarketing Data from Benign Prostatic Hyperplasia (BPH) patients**

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) including isolated reports. Frequency categories determined from post-marketing data refer to reporting rate rather than true 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**

### **Symptoms and Signs**

In volunteer studies 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 six months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

### **Treatment**

There is no specific antidote for dutasteride, therefore in cases of suspected overdosage, symptomatic and supportive treatment should be given as appropriate.

## **PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamics**

Dutasteride is a dual inhibitor of 5 alpha-reductase. It inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for male androgenetic alopecia (AGA).

#### ***Pharmacodynamic Effects***

The maximum effect of daily doses of dutasteride on the reduction on DHT is dose-dependent and is observed within one to two weeks. After one week and two 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 0.5 mg of dutasteride daily, the median decrease in DHT was 94% at one year and 93% at two years, and the median increase in serum testosterone was 19% at both one and two years. This is an expected consequence of 5 alpha-reductase inhibition.

In Alopecia patients, scalp and serum DHT levels decreased, and testosterone levels increased, in a dose-dependent fashion with dutasteride.

## **Pharmacokinetics**

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).

### ***Absorption***

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours.

Absolute bioavailability in man is approximately 60% relative to a 2 hour intravenous infusion. 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 (greater than 99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after one month and approximately 90% after three months. Steady state serum concentrations ( $C_{ss}$ ) of approximately 40 nanograms/mL are achieved after six months of dosing 0.5 mg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at six months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 nanograms/mL (range 0.4 to 14 nanograms/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

### ***Metabolism***

In vitro, dutasteride is metabolised by the human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

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-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The five human serum metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

### ***Elimination***

Dutasteride is extensively metabolised. 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 four

major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and six 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 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 three to nine 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 three to five weeks. At therapeutic concentrations, the terminal half-life of dutasteride is three to five weeks, and following repeat dosing of 0.5 mg/day, the slower clearance dominates and the total clearance is linear and concentration-independent. Serum concentrations remain detectable (greater than 0.1 nanograms/mL) for up to four to six months after discontinuation of treatment.

### ***Special Patient Populations***

- **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 C<sub>max</sub> 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. 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. 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 *Dosage and Administration, Warnings and Precautions and Contraindications*).

## Clinical Studies

### ***NUVANIV* monotherapy for Alopecia**

Study ALO106377 enrolled male subjects, 22-49 years of age, with male pattern hair loss (AGA Type IIIv, IV or V by NHC scale); 76 subjects were randomised to *NUVANIV* 0.5 mg and 77 subjects were randomised to placebo. All subjects in this study were Korean, demonstrating efficacy in an Asian patient population. Efficacy results revealed that hair counts (within a 1.0 cm<sup>2</sup> target area) were increased more from baseline in the *NUVANIV* group compared to the placebo group at 24 weeks, but not at 12 weeks (*see Table 1*). In addition, both the subject's assessment and an expert panel assessment observed less hair loss in the *NUVANIV* group compared to the placebo group at both 12 weeks and 24 weeks.

Study ARIA2004 (conducted in a largely Caucasian patient population in the US) compared placebo, finasteride 5 mg and four doses of dutasteride (0.05 mg, 0.1 mg, 0.5 mg and 2.5 mg) in the treatment of male pattern hair loss. 416 male subjects, 21-45 years of age with male pattern baldness (with AGA Type IIIv, IV or I by NHC scale) were randomised. Dutasteride 0.1 mg, 0.5 mg and finasteride 5 mg were significantly different from placebo for mean change in hair count (within a 5.1 cm<sup>2</sup> target area) from baseline at 12 weeks and at 24 weeks (*see Table 2*). Expert panel photographic review and investigator assessment of hair growth confirmed these results.

ARI114263 was a randomised, double-blind, double dummy, parallel group, 29-week study conducted at 39 centres in nine countries, which included Asian, Caucasian and Hispanic populations. The study randomised 917 male subjects, 20-50 years of age (with AGA Type IIIv, IV or V by NHC scale), and compared placebo, finasteride 1 mg and three doses of dutasteride (0.02 mg, 0.1 mg and 0.5 mg) in the treatment of androgenetic alopecia.

Primary efficacy endpoint in ARI114263 was hair growth defined as change from baseline in hair count at the vertex at 24 weeks. Dutasteride 0.1 mg, 0.5 mg and finasteride were significantly improved from placebo for mean change in hair count (within a 5.1 cm<sup>2</sup> target area) from baseline at 12 weeks and at 24 weeks (*see Table 3*). Only dutasteride 0.5 mg was superior to finasteride at 12 and 24 weeks (*see Table 3*).

Secondary endpoints included hair growth and restoration (terminal hair count and target area hair width assessed at 12 and 24 weeks), panel global photographic assessment, and Investigator Photographic Assessment Questionnaire (IPAQ) score. These results all confirmed the primary findings of the superiority of *NUVANIV* compared with placebo.

**Table 1. Study ALO106377; Hair Count (Target Area 1 cm<sup>2</sup>) (ITT Population)**

Parameter	Placebo Mean (SD) N=73	<i>NUVANIV</i> 0.5 mg Mean (SD) N=68
Baseline	144.3 (32.3)	148.1 (36.3)
<b>Week 12 (LOCF)</b>		
Hair count at Week 12	154.5 (36.9)	160.2 (36.7)
Change from baseline at Week 12	10.2 (19.0)	7.58 (22.7)
Mean difference from placebo at Week 12 [95% CI] p-value	-	-2.7 [-9.8, 4.5] 0.46 <sup>1</sup>
<b>Week 24 (LOCF)</b>		
Hair count at Week 24	149.6 (34.4)	162.3 (38.5)
Change from baseline at Week 24	4.7 (16.8)	12.2 (23.6)
Mean difference from placebo at Week 24 [95% CI] p-value	-	7.5 [0.8, 14.3] 0.032 <sup>1</sup>

CI = Confidence Interval; ITT = Intent-to-treat; LOCF=Last Observation Carried Forward; SD = Standard Deviation.

1. Unpaired t-test.

**Table 2. Study ARIA2004; Hair Count (Target Area 5.1 cm<sup>2</sup>) (ITT Population)**

Parameter	Placebo N = 64	Dutasteride		Finasteride 5.0 mg N = 70
		0.1 mg N = 72	<i>NUVANIV</i> 0.5 mg N = 68	
Baseline mean (SD)	920.3 (236.4)	907.8 (224.3)	927.5 (219.8)	902.1 (262.9)
<b>Week 12 (LOCF)</b>				
Adjusted mean change from baseline (SD)	-22.9 (73.8)	54.3 (83.0)	71.9 (69.1)	52.1 (95.7)
Adjusted mean difference from placebo (95% CI) p-value	-	77.2 (48.1, 106.4) <0.001	94.8 (65.0, 124.7) <0.001	75.0 (46.1, 103.8) <0.001
<b>Week 24 (LOCF)</b>				
Adjusted mean change from baseline (SD)	-29.6 (63.6)	72.3 (88.8)	95.5 (73.3)	73.2 (82.6)
Adjusted mean difference from placebo (95% CI) p-value	-	101.9 (74.2, 129.7) <0.001	125.1 (97.1, 153.2) <0.001	102.8 (75.3, 130.3) <0.001

CI = Confidence Interval; FIN = finasteride; ITT = Intent-to-treat; LOCF=Last Observation Carried Forward; SD = Standard Deviation.

**Table 3. Study ARI114263; Hair Count (Target Area 5.1 cm<sup>2</sup>) (ITT Population)**

Parameter	Placebo N=181	Dutasteride		Finasteride 1 mg N=179
		0.1 mg N=188	<i>NUVANIV</i> 0.5 mg N=184	
Baseline: Mean (SD)	760.9 (226.9)	721.3 (220.2)	767.5 (218.0)	763.8 (180.6)
<b>Week 12 (LOCF)</b>				
Adjusted mean change from baseline (SD)	-4.0 (86.6)	59.6 (95.5)	82.3 (98.2)	50.9 (78.7)
Adjusted mean difference from placebo (98.33% CI), p-value	-	63.6 (39.3, 87.9) <0.001	86.4 (61.9, 110.9) <0.001	55.0 (29.8, 80.1) <0.001
Adjusted mean difference from FIN (98.33% CI), p-value	-	8.7 (-16.4, 33.7) 0.41	31.4 (6.2, 56.6) 0.003	-
<b>Week 24 (LOCF)</b>				
Adjusted mean change from baseline (SD)	-4.9 (104.3)	63.0 (106.0)	89.6 (103.0)	56.5 (99.9)
Adjusted mean difference from placebo (98.33% CI), p-value	-	67.9 (41.6, 94.2) <0.001	94.4 (67.8, 121.0) <0.001	61.4 (34.4, 88.4) <0.001
Adjusted mean difference from FIN (98.33% CI), p-value	-	6.5 (-20.1, 33.1) 0.56	33.0 (6.1, 60.0) 0.003	-

CI = confidence interval; FIN = finasteride; ITT = Intent-to-treat; LOCF=Last Observation Carried Forward; SD = Standard Deviation.

### Cardiac failure

In a 4-year comparison of dutasteride coadministered with tamsulosin and dutasteride or tamsulosin monotherapy in men with BPH (the CombAT study), the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: dutasteride, 4/1623 (0.2%) and tamsulosin, 10/1611, (0.6%). The relative risk estimate for time to first cardiac failure event was 3.57 [95% CI

1.17, 10.8] for combination treatment compared to dutasteride monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy.

In a 4-year chemoprevention, comparison study of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride (30/4105, 0.7%) versus placebo (16/4126, 0.4%) for a relative risk estimate for time to first cardiac failure event of 1.91 [95% CI 1.04, 3.50]. In a post-hoc analysis of concomitant alpha blocker use, there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking dutasteride and an alpha blocker concomitantly: dutasteride and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), placebo and no alpha blocker (15/2727, 0.6%). No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (*see Warnings and Precautions*).

### **Prostate cancer and high grade tumours**

In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), 6,706 subjects had prostate needle biopsy data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81).

There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%) (p=0.15). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the dutasteride group (n=17, 0.5%) and the placebo group (n=18, 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the dutasteride group (n=12, 0.5%) compared with the placebo group (n=1, <0.1%) (p=0.0035). There are no data available on the effect of dutasteride beyond 4 years in men at risk of developing prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the dutasteride group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively). In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were (n=8, 0.5%) for dutasteride, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy (*see Warnings and Precautions*).

The results of an epidemiological, population-based study (n=174,895) in community practice settings show that the use of 5-ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality (hazard ratio adjusted for competing risks:

0.85, 95% CI 0.72, 1.01) when compared with the use of alpha-blockers. Similar results were reported in an epidemiological study (n=13,892) of men with prostate cancer in the UK (adjusted hazard ratio for prostate cancer mortality for 5-ARI users versus non-users: 0.86; 95% CI 0.69, 1.06). A prospective cohort study, the Health Professional's Follow-up Study (n=38,058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69).

### **Effects on prostate specific antigen (PSA) and prostate cancer detection**

In the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL, dutasteride treatment caused a decrease in mean serum PSA by approximately 50% after six months of treatment with a large variability (standard deviation of 30%) among patients. The PSA suppression observed at six months was similar in men who did or who did not develop biopsy-detectable prostate cancer during the study (*see Warnings and Precautions*).

### **Incidence of breast cancer**

Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6,780 controls) and the other in a UK (n=398 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5-ARIs (*see Warnings and Precautions*). Results from the first study did not identify a positive association for male breast cancer (relative risk for  $\geq 1$ -year of use before breast cancer diagnosis compared with  $< 1$ -year of use: 0.70; 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5-ARIs compared with non-use was 1.08; 95% CI 0.62, 1.87).

The relationship between long-term use of dutasteride and male breast cancer has not been established.

### **Pre-clinical Safety Data**

Dutasteride has been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5-alpha-reductase inhibitors.

#### *Carcinogenesis, mutagenesis*

Dutasteride showed no evidence of genotoxicity in a wide range of *in vitro* and *in vivo* tests. In a carcinogenicity study in rats, there was an increase in benign interstitial cell tumours in the testis at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

#### *Reproductive toxicology*

Dutasteride produced a reversible decrease in fertility in male rats consistent with the pharmacological activity of 5-alpha-reductase inhibition on accessory reproductive organs. This is considered to have no clinical relevance as there was no effect on sperm development, concentration or motility. Feminisation of the external genitalia was noted in male foetuses of female rats and rabbits orally dosed with dutasteride. However, i.v. administration of dutasteride to pregnant Rhesus monkeys during embryofetal development at doses of up to 2010 nanograms/animal/day did not produce adverse maternal or fetal toxicity. This dose represents a multiple of at least 186-fold (nanograms/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100% absorption) from a dutasteride-treated man.

## **PHARMACEUTICAL PARTICULARS**

### **List of Excipients**

**Capsule contents:** monodiglycerides of caprylic/capric acid; butylated hydroxytoluene

**Capsule shell:** gelatin; glycerol; titanium dioxide; iron oxide red, black printing ink.

Medium chain triglycerides and lecithin as capsule lubricants.

### **Incompatibilities**

Not applicable.

### **Shelf Life**

The expiry date is indicated on the packaging.

### **Special Precautions for Storage**

Do not store above 30°C.

### **Nature and Contents of Container**

PVC/PVDC blisters.

### **Instructions for Use/Handling**

Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules (*see Warnings and Precautions and Pregnancy and Lactation*). If contact is made with leaking capsules the contact area should be washed immediately with soap and water.

Not all presentations are available in every country.

Manufacturer:

Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716-1016, USA

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