

PRODUCT MONOGRAPH

# Liposteride™

Liposomal Dutasteride Topical Serum

Serum (Lotion), 50 gr

Type I and II of 5-Alpha-reductase's Inhibitor



No. 16, Mirhadi St., Jouybar St.,  
Fatemi Sq., Tehran, Iran

Date of Revision:

August 12, 2025

©2025 Sushiyant Derma Biotech, All Rights Reserved

® LIPOSTERIDE is a registered trademark, used under license by Sushiyant Derma Biotech

## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE .....	3
CONTRAINDICATIONS .....	3
WARNINGS AND PRECAUTIONS .....	4
ADVERSE REACTIONS .....	4
DRUG INTERACTIONS.....	5
DOSAGE AND ADMINISTRATION.....	7
OVERDOSAGE .....	8
ACTION AND CLINICAL PHARMACOLOGY .....	8
STORAGE AND STABILITY .....	10
SPECIAL HANDLING INSTRUCTIONS .....	10
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	10
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>12</b>
PHARMACEUTICAL INFORMATION.....	12
CLINICAL TRIALS .....	12
DETAILED PHARMACOLOGY .....	14
TOXICOLOGY .....	15
REFERENCES .....	17

# Liposteride™

Liposomal Dutasteride Topical Serum

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Liposomal Serum (Lotion) 0.2% w/w For Men (Black) 0.1% w/w For Women (White)	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

LIPOSTERIDE® (Topical Liposomal Dutasteride) is indicated for the treatment of **androgenetic alopecia (male and female pattern hair loss)** in adults. It reduces scalp dihydrotestosterone (DHT) by inhibiting both type I and II 5 $\alpha$ -reductase isoenzymes, slowing hair follicle miniaturization and promoting hair density preservation.

#### Limitations of Use:

- Efficacy and safety of LIPOSTERIDE® have not been established in patients under 18 years of age and generally such administration is not recommended.
- Upon irregular use of LIPOSTERIDE® systemic effects may occur; caution is warranted in patients at risk for dutasteride- related systemic adverse events.

### CONTRAINDICATIONS

LIPOSTERIDE™ is contraindicated for use in women who are pregnant or may become pregnant (risk of teratogenicity to a male fetus, see WARNINGS AND PRECAUTIONS, Exposure of Women-Risk to Male Fetus).

LIPOSTERIDE™ is contraindicated in patients with known hypersensitivity to dutasteride, other 5 alpha-reductase inhibitors, or any component of the preparation.

LIPOSTERIDE™ is contraindicated for use in children.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### **LIPOSTERIDE™ is For External Use Only:**

Not for ophthalmic, oral, or intravaginal use.

#### **Systemic Absorption:**

Although LIPOSTERIDE™ is formulated for topical application, percutaneous absorption can occur particularly with chronic use over large areas or on compromised skin. In such cases, systemic effects similar to oral dutasteride (provided in the following sections) are possible.

#### **Exposure of Women-Risk to Male Fetus:**

Dutasteride is absorbed through the skin. Therefore, women who are pregnant or may be pregnant should not handle LIPOSTERIDE™ serum due to risk of external genital malformations in male fetuses.

#### **Blood Donation:**

Patients should not donate blood for at least 6 months after stopping therapy using LIPOSTERIDE™ to avoid exposure in pregnant transfusion recipients.

#### **Sexual and Hormonal Effects:**

Reports from systemic use of Dutasteride include decreased libido, erectile dysfunction, ejaculation disorders, and changes in semen parameters. Risk with topical therapy using LIPOSTERIDE™ is much lower but not excluded.

#### **Breast Tissue Changes:**

Rare cases of male breast tenderness, enlargement, or malignancy have been reported with systemic use of dutasteride. Patients should promptly report if any breast changes.

#### **Hepatic Impairment:**

Dutasteride is extensively metabolized by CYP3A4; caution is advised in patients with liver disease while administering LIPOSTERIDE™.

## ADVERSE REACTIONS

### **Adverse Drug Reaction Overview**

The following adverse reactions for LIPOSTERIDE™ could be justified from systemic dutasteride experience, license-holder developmental testing and emerging topical studies.

**Common (> 1%) systemic-type effects** (seen rarely with topical use):

- Decreased libido
- Erectile dysfunction
- Ejaculation disorders
- Breast tenderness or enlargement

**Local adverse effects:**

- Application site irritation, erythema, pruritus, or dermatitis

- Rare folliculitis or seborrheic dermatitis flare

**Post-marketing/ systemic reports (rare):**

- Allergic skin reactions (rash, urticaria, angioedema)
- Mood changes (including depressed mood)
- Testicular discomfort or swelling

**Post-Market Adverse Drug Reactions**

*The following events have been reported voluntarily during post-market use of oral dutasteride dosage forms. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to drug exposure or a combination of these factors.*

*Very rare* - depressed mood, allergic reactions, including rash, pruritus, urticaria, localized edema, serious skin reactions and angioedema, testicular pain, and testicular swelling.

*Rare* - body hair loss and hypertrichosis.

**DRUG INTERACTIONS**

**Overview**

Care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors such as ritonavir, **ketoconazole**, verapamil, diltiazem, cimetidine, troleandomycin, and ciprofloxacin. Based on the *in vitro* data, blood concentrations of dutasteride may increase in the presence of CYP3A4 inhibitors.

Dutasteride does not inhibit the *in vitro* metabolism of model substrates for the major human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL, 25 times greater than steady-state serum concentrations in humans. *In vitro* studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein binding sites, nor do these model compounds displace dutasteride.

**Drug-Drug Interactions**

**Cytochrome P450 Inhibitors:** LIPOSTERIDE™ is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. The effect of potent CYP3A4 inhibitors on dutasteride has not been studied. Because of the potential for drug-drug interactions, use caution when prescribing LIPOSTERIDE™ to patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ketoconazole).

**Other 5-Alpha Reductase Inhibitors:** Avoid concomitant use with other systemic 5 $\alpha$ -reductase inhibitors like Finasteride oral tablets unless medically justified.

**Topical Minoxidil:** No known interactions with topical minoxidil; concomitant use has been reported without major safety signals.

**Digoxin:** In a study of 20 healthy volunteers, oral dutasteride did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

**Warfarin:** In a study of 23 healthy volunteers, 3 weeks of treatment with oral dutasteride 0.5 mg/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.

**Alpha-Adrenergic Blocking Agents:** In a single sequence, crossover study in healthy volunteers, the administration of tamsulosin or terazosin in combination with oral dutasteride had no effect on the steady state pharmacokinetics of either alpha adrenergic blocker. The percent change in DHT concentrations was similar for oral dutasteride alone compared with the combination treatment.

**Calcium Channel Antagonists:** In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was noted when co-administered 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 co administered 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 is recommended.

**Cholestyramine:** Administration of a single 5 mg dose of oral dutasteride followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

**Other Concomitant Therapy:** Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in the 3 Phase III pivotal efficacy studies receiving oral dutasteride were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of oral dutasteride and concurrent therapy when it 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.

### **Drug-Food Interactions**

**Dutasteride absorption is not affected by food.** The effects of CYP3A4 inhibitors found in foods on dutasteride pharmacokinetics have not been studied. Care should be taken when

administering dutasteride to patients who chronically consume CYP3A4 inhibitors found in foods and beverages such as grapefruit juice.

### **Drug-Herb Interactions**

The effects of herbal remedies on the pharmacokinetics of dutasteride have not been studied. Care should be taken when administering dutasteride to patients who chronically consume herbal remedies containing CYP3A4 inhibitors (e.g., milk thistle) or CYP3A4 inducers (e.g., St. John's wort).

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

#### **Adults**

Take 1 ml (equivalent to **once filling** of glass dropper) of LIPOSTERIDE™ serum and spread it as an even layer to the affected scalp area **once daily**.

Ensure the scalp is clean and dry before application.

Wash hands thoroughly after use.

Avoid washing or wetting hair for at least 6 hours after application.

~~LIPOSTERIDE™ may be taken with or without food (see WARNINGS AND PRECAUTIONS, Drug-Food Interactions).~~

Although an improvement in symptoms may be observed after 4 months in some patients, it can take up to 6 months before a response to the treatment can be achieved (See CLINICAL TRIALS).

#### **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, and due to topical delivery in LIPOSTERIDE™ such recovery is much lower and no adjustment in dose 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 and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease.

#### **Missed Dose**

If a dose is missed the regular 1 ml dropper can be taken at the next scheduled dose. Extra serum taken for missed doses are not necessary.

## OVERDOSAGE

**For management of a suspected drug overdose, contact your regional Poison Control Centre.**

In volunteer studies of oral dutasteride, 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, oral 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. Therefore, topical overdose by using LIPOSTERIDE™ is unlikely. Excessive application may increase risk of systemic absorption and related adverse events.

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

## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

Dutasteride, a synthetic 4-azasteriod compound, inhibits the conversion of testosterone to 5  $\alpha$ -dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. In AGA, elevated DHT within hair follicles leads to progressive miniaturization. Testosterone is converted to DHT by the enzyme 5  $\alpha$ -reductase, which exists as 2 isoforms, Type I and Type II. Both Type I and Type II isoenzymes are present in the hair follicles (specifically, dermal papilla cells). The Type I isoenzyme is also responsible for testosterone conversion in the skin and liver. It has been observed that compared to normal hair cycle, accumulation of DHT leads to progression of Androgenic alopecia which local delivery of dutasteride reduces follicular DHT and helps preserve hair shaft diameter and density while the liposomal structure enhance penetration via follicular delivery.

Dutasteride is a competitive and specific inhibitor of both Type I and Type II 5  $\alpha$ -reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under *in vitro* and *in vivo* conditions and is extremely slow. Dutasteride lowers DHT levels and leads to preserve hair shaft diameter and density after consistent local action of the molecule. Dutasteride does not bind to the human androgen receptor.

### **Pharmacodynamics**

When Dutasteride administered orally, it produces a rapid and sustained reduction of serum DHT levels by >90% within 2–4 weeks of therapy, accompanied by compensatory increases in serum testosterone that remain within the physiological range. Intraprostatic and scalp tissue concentrations of DHT are reduced in parallel, which is the mechanistic basis for its use in hair disorders. These systemic findings provide a pharmacological reference framework for the topical formulation.

The liposomal topical formulation in LIPOSTERIDE™ is designed to optimize follicular delivery while minimizing systemic exposure. Liposomes enhance penetration into the pilosebaceous unit, the key site of 5 $\alpha$ -reductase activity in the scalp, allowing for targeted suppression of follicular DHT. This local mechanism reduces the risk of systemic endocrine effects while maintaining therapeutic efficacy at the scalp level.

### **Clinical Pharmacodynamic Observations in Topical Use**

In sponsor-conducted clinical evaluations, topical liposomal dutasteride demonstrated statistically significant improvements in multiple scalp parameters of hair growth and cycling which demonstrates a pharmacodynamic signature consistent with its known mechanism of action as a dual 5 $\alpha$ -reductase inhibitor:

- Localized reduction of DHT in scalp tissue.
- Reversal of follicular miniaturization.
- Enhancement of terminal hair counts and density, translating into visible cosmetic benefit.
- Preservation of hair shaft thickness and integrity.
- Maintenance of normal anagen–telogen balance, avoiding disruption of physiological cycling.

These findings align with the systemic pharmacology of oral dutasteride but highlight the advantage of targeted follicular delivery with topical administration achieving clinically meaningful improvements in hair density and appearance, while minimizing systemic endocrine exposure.

### **Pharmacokinetics**

**Absorption:** Oral dutasteride is rapidly absorbed with peak concentrations occurring at 1 to 3 hours and absorption is not affected by food. Absolute bioavailability is approximate 60% relative to a 2-hour intravenous infusion. For the case of topical LIPOSTERIDE™, Liposomal delivery enhances follicular penetration while minimizing systemic exposure.

**Distribution:** Dutasteride has a large volume of distribution (300-500 L) and is highly bound to proteins in plasma (> 99.5%). The half-life of dutasteride is 3 to 5 weeks. Steady state serum concentrations (C<sub>ss</sub>) of approximately 40 ng/mL are achieved after 6 months of dosing with dutasteride 0.5 mg once daily. Similarly for the case of topical delivery, Dutasteride concentrates in pilosebaceous units with minimal plasma levels compared to oral dosing.

**Metabolism:** Dutasteride is extensively metabolized in humans. Studies showed that CYP3A4 isoenzymes are involved in metabolism of dutasteride.

**Excretion:** Dutasteride and its metabolites were excreted mainly in feces. Only trace amounts of unchanged dutasteride were found in urine (< 1%) (see DETAILED PHARMACOLOGY).

### **Special Populations and Conditions**

**Geriatrics:** No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in subjects between the ages of 24- and 87-years following administration of systemic dutasteride. According to the results of studies for the case of systemic administration, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in men older than 70 years); but no overall differences in safety or efficacy were observed between elder patients and younger patients.

**Gender:** LIPOSTERIDE™ is not indicated for use in pregnant women (see WARNINGS AND PRECAUTIONS).

**Race:** The effect of race on LIPOSTERIDE™ pharmacokinetics has not been studied.

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

**Renal Insufficiency:** 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, especially in the case of topical delivery.

## STORAGE AND STABILITY

Store between 15°C and 30°C. Keep container tightly closed and away from heat or direct sunlight. Do not freeze the product. Keep out of reach of children. Shake well before use.

## SPECIAL HANDLING INSTRUCTIONS

Dutasteride is absorbed through the skin; therefore, pregnant women and children must avoid contact with leaking serum. If contact is made with leaking serum, the contact area should be washed immediately with soap and water (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

## DOSAGE FORMS, COMPOSITION AND PACKAGING

LIPOSTERIDE™ are Yellowish milky and thick serum provided in glass bottles of 50 gr together with glass dropper and sucker cap.

Each gram for topical administration contains 2 mg of dutasteride in customized product of males and 1 mg in customized product of female. In this serum. Dutasteride is dissolved in ethanol, encapsulated within the bilayer of liposome structures and the resulted liposomal particles dispersed in a hydrophilic gel based on Carbomer 940.

The following non-medicinal ingredients are contained in LIPOSTERIDE™ serum:  
Soybean lecithin, dry ginseng extract, sodium lauryl ether sulfate, caffeine, nicotinamide,  
citric acid monohydrate, tri-sodium citrate dihydrate, glycerin, triethanolamine, methyl and  
propyl paraben.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

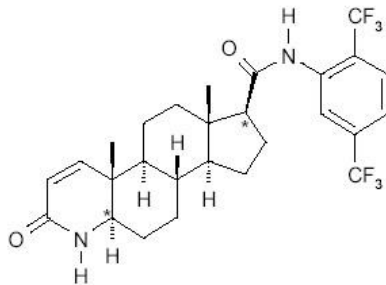
#### Drug Substance

Proper name: dutasteride

Chemical name: (5 alpha, 17 beta)-N-{2,5-bis(trifluoromethyl)phenyl}- 3-oxo -4-azaandrost-1-ene-17- carboxamide

Molecular formula and molecular mass: C<sub>27</sub>H<sub>30</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>, 528.5

Structural formula:



Physicochemical properties: Dutasteride is a white to pale yellow powder with a melting point of 242 to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL) and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

### CLINICAL TRIALS

#### Overview

The efficacy and safety of dutasteride in the treatment of androgenetic alopecia (AGA) have been investigated in a range of clinical settings, including oral, topical, and injectable formulations. Oral dutasteride has been extensively evaluated in Phase II and III clinical trials, establishing its superior efficacy over finasteride and placebo in male AGA. More recently, topical formulations and mesotherapy approaches have been explored, aiming to provide localized follicular DHT suppression while minimizing systemic exposure and related adverse effects.

#### Topical Dutasteride – Sponsor-Supported Trial

A sponsored Iranian clinical study (IRCT: 40013751001) was performed to evaluate the efficacy and tolerability of **topical liposomal dutasteride serum (0.1% w/w, 1 mL daily)** in women with female-pattern AGA. The trial also investigates the potential additive effect of combining topical dutasteride with low-level scalp laser therapy. Early safety evaluations have confirmed that the investigational topical product is well-tolerated, with

no unexpected adverse findings. Final efficacy data are pending, but the trial is expected to provide region-specific clinical support for topical dutasteride in female patients. Sponsor-provided clinical data demonstrated significant improvements in several key efficacy parameters:

- **Hair Counts and Density:** Terminal hair count and terminal hair density increased significantly from baseline at follow-up intervals, corresponding to visible regrowth and greater scalp coverage. Total hair count and overall density also increased, confirming broad stimulation of follicular activity.
- **Hair Maturation:** A reduction in vellus hair rate with a reciprocal increase in terminal hair rate was observed, supporting reversal of follicular miniaturization — a central pathologic process in AGA.
- **Follicular Units:** A significant reduction in single-hair follicular units was recorded, consistent with their conversion into multi-hair follicular units, a marker of healthier follicular cycling and more robust scalp appearance.
- **Hair Cycle Dynamics:** Anagen density significantly increased during therapy, confirming stimulation of the active growth phase. No significant changes were observed in telogen-related parameters, suggesting maintenance of a balanced hair cycle without adverse disruption.
- **Hair Shaft Quality:** Mean and cumulative hair thickness measures did not differ significantly across timepoints, indicating that the treatment promotes regrowth without compromising shaft caliber or quality.

Together, these findings support clinical claims of enhanced scalp density, reversal of miniaturization, and sustained hair health under topical dutasteride therapy.

### **Topical Dutasteride – International Experience**

An exploratory clinical trial (NCT05599243) investigated **topical dutasteride 0.15% O/W emulsion** in men with AGA. Daily application resulted in statistically significant improvements in hair density compared to placebo, with minimal systemic absorption as determined by plasma measurements. The favorable safety profile supports the potential of topical dutasteride as a localized treatment option with reduced risk of endocrine side effects associated with systemic exposure.

Additional studies of injectable and mesotherapy-based topical delivery are also underway. For example, a Brazilian study (NCT06110377) compares two techniques of dutasteride mesotherapy administration (needle injections versus tattoo machine-assisted delivery) in 60 male subjects with mild to moderate AGA. This trial is expected to provide insights into procedural optimization of local dutasteride delivery to the scalp.

### **Oral Dutasteride – Translational Reference Data**

Multiple pivotal trials have demonstrated the efficacy of **oral dutasteride 0.5 mg daily** in male AGA, providing a pharmacological benchmark for the topical route:

- A dose-ranging, placebo-controlled study (NCT01231607) found that oral dutasteride (0.5 mg) significantly improved hair growth over 24 weeks compared with placebo, with greater suppression of DHT levels than lower oral doses.
- A long-term trial (NCT01831791) confirmed that oral dutasteride was superior to finasteride in increasing hair growth index (HGI) scores and patient-reported satisfaction scales, indicating higher perceived benefit with dutasteride therapy.

- A Phase III Korean study (NCT00441116) demonstrated significant improvements in hair growth in men with Norwood–Hamilton types IIIv, IV, and V vertex baldness after 6 months of 0.5 mg oral dutasteride compared with placebo.

Together, these trials confirm dutasteride’s superior efficacy over finasteride and placebo in androgenetic alopecia and establish its pharmacodynamic basis (robust DHT suppression at the follicular level). These findings are directly translatable to topical use, given the shared mechanism of action, but topical administration is designed to achieve these benefits with substantially lower systemic drug exposure.

Clinical investigations of topical dutasteride, including ongoing sponsor-supported studies and international exploratory trials, indicate that localized follicular delivery of dutasteride enhances hair density and reverses miniaturization while preserving a favorable safety profile. Oral trial data provide strong pharmacological validation of efficacy, while topical and mesotherapy formulations represent an important advance in balancing efficacy with minimized systemic risk.

## DETAILED PHARMACOLOGY

In LIPOSTERIDE™, Dutasteride is administered locally as a hydrophilic serum. According to In-Vitro Release profile of LIPOSTERIDE™, Following topical administration of 2 or 1 mg dutasteride, the absolute bioavailability is approximately 10% relative to a 2-hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (> 99.5%). Following daily topical dosing, dutasteride serum concentrations will be negligible and non-detectable.

Steady state serum concentrations ( $C_{ss}$ ) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day, but it is far below the amount which could be reached in topical application.

*In vitro*, dutasteride is metabolized by the human cytochrome P450 enzyme CYP3A4 to two minor monohydroxylated metabolites, but is not metabolized by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6. In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The 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.

Dutasteride is extensively metabolized in humans. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as 4 major

metabolites comprising 39%, 21%, 7%, and 7% each of 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. Therefore, in the case of topical administration due to limited absorption, all the mentioned metabolites are extremely low and could not be detectable using the established methods of quantification.

Regarding the data provide for the oral dosage form of Dutasteride, the terminal half-life of dutasteride is 3 to 5 weeks. Serum DHT concentrations which correlate to clinical effect, return to baseline (no clinical effect) within approximately 4 months after discontinuation of treatment.

Dutasteride pharmacokinetics can be described as first order absorption process and two parallel elimination pathways, one saturable (concentration dependent) and one non-saturable (concentration independent). At low serum concentrations (less than 3 ng/mL) provided through dermal and follicular absorption of LIPOSTERIDE™, dutasteride is cleared rapidly by both the concentration dependent and concentration independent elimination pathways.

## **TOXICOLOGY**

### **Acute Toxicology**

Acute oral toxicity studies in animals demonstrated that dutasteride has a very wide safety margin, with maximum non-lethal doses (MNL) exceeding 2,000 mg/kg in mice and 1,500 mg/kg in rats, equivalent to exposures hundreds of thousands of times higher than the anticipated therapeutic human dose. Intraperitoneal administration produced local irritant effects, attributed primarily to the vehicle system and exacerbated by the physicochemical properties of dutasteride; no systemic MNL could be determined via this route. Importantly, no unequivocal target organ toxicity was observed at acutely high doses, supporting the conclusion that acute systemic toxicity is unlikely under clinical conditions.

For the topical liposomal formulation, systemic exposure is expected to be substantially lower than with oral dosing, given the localized delivery to the scalp and the drug's poor aqueous solubility. Based on the oral safety margin and limited absorption, the risk of acute systemic toxicity from topical application is considered negligible. Any local adverse effects observed in animal and clinical studies have been limited to mild erythema (redness) at the application site regarding the sensitization studies performed for LIPOSTERIDE™. Findings of reduced prostate and seminal vesicle size in male animals are considered to reflect the expected pharmacologic activity of dutasteride via DHT suppression, rather than evidence of intrinsic acute toxicity.

### **Long Term Toxicity**

Repeat-dose oral toxicity studies in rats (5–26 weeks, up to 500 mg/kg/day in males and 100–30 mg/kg/day in females) and in dogs (26–53 weeks, up to 50–10 mg/kg/day) demonstrated treatment-related changes predominantly in the reproductive and endocrine systems. These findings, including reduced prostate and seminal vesicle size, epithelial atrophy in the epididymis, decreased ovary and uterus weights, and cyclic shifts in estrous

activity, are consistent with the pharmacological suppression of dihydrotestosterone (DHT) via dual inhibition of  $5\alpha$ -reductase. In dogs, reversible changes in thyroid weight and histology, as well as alterations in pituitary and adrenal morphology, were observed at high exposure levels. Importantly, no significant impairment of spermatogenesis was recorded, and observed changes were generally reversible. Centrally mediated non-specific signs of toxicity occurred at exposures several hundred-fold higher than clinical serum levels achieved with oral therapy. As expected from the mechanism of action, a formal no-observed-adverse-effect level (NOAEL) could not be established due to consistent endocrine-related effects, though no other toxicologically relevant findings were present at exposure margins far exceeding anticipated human exposure.

For the topical liposomal formulation, systemic exposure is expected to remain substantially lower than that associated with oral administration, given the localized scalp delivery and limited percutaneous absorption. Therefore, the likelihood of reproducing systemic endocrine effects seen in animal oral studies is low under clinical use conditions. Special dermal and ocular toxicity studies support the local tolerability profile: acute dermal application in rabbits produced only slight, reversible irritancy with an estimated dermal  $LD_{50} > 2,000$  mg/kg, and dermal absorption studies confirmed measurable but limited systemic uptake even at supratherapeutic doses. Dutasteride demonstrated slight ocular irritancy in rabbits, resolving within 72 hours, and showed minimal erythema (redness) evidence of dermal sensitization in guinea pigs. In vitro assessments indicated no hemolytic potential and minimal vascular irritation. Collectively, these data support that topical administration is unlikely to elicit systemic toxicities at therapeutic doses, with potential local adverse effects limited to mild, reversible skin or eye irritation.

### **Reproduction and Teratology**

In oral fertility studies, male rats administered dutasteride at doses of 0.05 to 500 mg/kg/day for up to 31 weeks showed dose- and time-dependent reductions in fertility, associated with decreased weights of the prostate, seminal vesicles, and epididymides, and corresponding histopathological changes. These findings are consistent with the expected pharmacological suppression of dihydrotestosterone (DHT) through  $5\alpha$ -reductase inhibition. Importantly, testicular histology, sperm counts, and motility were unaffected, suggesting that fertility reductions were secondary to impaired seminal secretion and failure of copulatory plug formation, a mechanism not clinically relevant in humans.

Female rat fertility studies demonstrated a no-observed-adverse-effect level (NOAEL) of 0.05 mg/kg/day for maternal effects, though fetal body weight reductions and feminization of male fetuses occurred at  $\geq 2.5$  mg/kg/day. Oral embryofetal development studies in rats confirmed these findings, with feminization of male fetuses and reversible delays in ossification observed across tested dosages. Rabbit studies similarly demonstrated feminization of male fetuses at all oral dose levels tested (0.05 to 200 mg/kg/day), consistent with dutasteride's mechanism of action.

In humans, dutasteride is detectable in semen at low concentrations following chronic oral administration, with maximal levels of approximately 14 ng/mL. An intravenous embryofetal development study in rhesus monkeys using exposure multiples  $> 180$ -fold higher than potential human seminal transfer showed no evidence of maternal or fetal toxicity, nor feminization of male offspring. Dutasteride is highly bound to proteins in semen ( $>96\%$ ), reducing the amount available for vaginal absorption.

Oral pre- and post-natal studies in rats confirmed pharmacologic effects on male offspring, including feminization (decreased anogenital distance), hypospadias, reduced fertility, and prostatitis at  $\geq 2.5$  mg/kg/day. In females, earlier onset of vaginal patency was observed, consistent with androgen suppression. These findings reflect class-related effects of 5 $\alpha$ -reductase inhibition rather than direct systemic toxicity; that the reason why the strength of customized product for women (0.1% w/w) is half the strength of its for men (0.2% w/w).

For the topical liposomal formulation, systemic exposure is expected to be significantly lower than that observed with oral dosing, minimizing reproductive risks under therapeutic use. However, the potential for male fetal harm remains, as dutasteride can be absorbed through the skin. As with oral formulations, topical dutasteride is contraindicated in women who are pregnant or may become pregnant, and women of childbearing potential should avoid direct contact with the drug product or treated scalp areas.

### **Mutagenicity and Carcinogenicity**

Comprehensive genetic toxicology testing has shown no evidence that dutasteride or its major metabolites are mutagenic or clastogenic. Dutasteride and its 4'-hydroxy metabolite were negative in the Ames bacterial reverse mutation assay at concentrations up to 5,000  $\mu$ g/plate, both with and without metabolic activation. The 1,2-dihydro metabolite of dutasteride similarly showed no mutagenic activity in a miniwell Ames test at concentrations up to 800  $\mu$ g/well. In vitro assays in Chinese Hamster Ovary cells found no evidence of clastogenicity at concentrations up to 1,150  $\mu$ g/mL, and in vivo rat micronucleus studies at dose levels up to 1,500 mg/kg/day over six days confirmed the absence of mutagenic or clastogenic potential.

Carcinogenicity studies were conducted in mice and rats at exposures many-fold higher than anticipated clinical levels. In a 2-year mouse study, an increased incidence of benign hepatocellular adenomas was noted in female mice at the highest dose tested (250 mg/kg/day, approximately 290-fold the expected human clinical exposure). In a 2-year rat study, Leydig cell adenomas and hyperplasia were observed in males at high doses ( $\geq 7.5$  mg/kg/day), consistent with compensatory increases in luteinizing hormone secondary to 5 $\alpha$ -reductase inhibition. These findings are interpreted as species-specific endocrine-mediated responses and are not considered directly predictive of human risk.

For the topical liposomal formulation, systemic exposure is expected to remain significantly lower than oral administration, limiting the potential for carcinogenic effects. The absence of genotoxic activity in standard mutagenicity assays, together with the mechanistic explanation of endocrine-mediated proliferative changes at supratherapeutic exposures in animals, indicates that topical dutasteride does not present a mutagenic or carcinogenic risk at clinically relevant doses.

### **REFERENCES**

1. Andriole GL, Kirby R. Safety and tolerability of the dual 5 alpha-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol* 2003;44(1): 82-88.

2. Debruyne F, Barkin J, van Erps P, Reis M, Tammela TL, Roehrborn C. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Euro Urol* 2004;46(4):488-494.
3. Frye SV, Bramson HN, Hermann DJ, Lee FW, Sinhababu AD, Tain G. Discovery and development of GG745, a potent inhibitor of both isozymes of 5 alpha-reductase. *Pharm Biotechnol* 1998;11:393-422.
4. Gisleskog PO, Hermann G, Hammarlund-Udenaes M, Karlsson MO. The pharmacokinetic modelling of GI198745 (dutasteride), a compound with parallel linear and nonlinear elimination. *Br J Clin Pharmacol* 1999;47(1):53-58.
5. Graul A, Silvestre J, Castaner J. Dutasteride. Steroid 5 alpha-reductase inhibitor, treatment of BPH. *Drugs Future* 1999;24(3):246-253.
6. Iehle C, Radvanyi F, Gil Diez de MS, Ouafik LH, Gerard H, Chopin D, et al. Differences in steroid 5alpha-reductase iso-enzymes expression between normal and pathological human prostate tissue. *J Steroid Biochem Mol Biol* 1999 Mar;68(5-6):189-95.
7. Roehrborn CG, Lukkarinen O, Mark S, Siami P, Ramsdell J, Zinner N. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int* 2005 Sep;96(4):572-7.
8. Roehrborn CG, Marks LS, Fenter T, Freedman S, Tuttle J, Gittleman M, et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. *Urology* 2004; 63 (4), 2004;709-715.
9. Stuart JD, Lee FW, Simpson ND, Kadwell SH, Overton LK, Hoffman CR et al. Pharmacokinetic parameters and mechanisms of inhibition of rat type 1 and 2 steroid 5 alpha-reductases: determinants for different *in vivo* activities of GI198745 and finasteride in the rat. *Biochem Pharmacol* 2001; 62(7):933-942.
10. Thomas LN, Lazier CB, Gupta R, Norman RW, Troyer DA, O'Brien SP, et al. Differential alterations in 5alpha-reductase type 1 and type 2 levels during development and progression of prostate cancer. *Prostate* 2005 May 15;63(3): 231-9.