



Dutasteride Consent Form

Dutasteride (Avodart in the USA) and (Avolve in Europe)

Dutasteride is an oral medication, manufactured by Glaxo, which blocks the conversion of testosterone to dihydrotestosterone (DHT), the form of the hormone that causes male pattern baldness. It does this by inhibiting the action of the type I and type II 5-alpha reductase enzyme that is present in higher concentration in and around, the hair follicles of balding men with androgenetic alopecia.

The medication causes a significant drop in both scalp and blood levels of DHT. Its effectiveness is felt to be related to both of these factors. In patients taking finasteride 1-mg/day, serum DHT levels decreased by 68.4% and serum testosterone levels actually increased by 9.1% but remained within the normal range. In patients taking dutasteride 0.5 mg/day serum DHT levels decreased by 85% in one week and 90% by two weeks. After one year of taking dutasteride 0.5mg/day serum DHT levels decreased by 94% and testosterone levels increased by 19%, but the testosterone levels remained within physiologic limits. Thyroid Stimulating Hormone (TSH) levels increased 12.4% at 52 weeks and luteinizing hormone (LH) increased by 12% at 6 months and 19% at 12 months. We do not know what the long term consequences will be of the increase in testosterone, TSH, or LH

Dutasteride is marketed for use in symptomatic benign prostate hyperplasia (enlargement) in men over 50 (the prostate also has the 5-alpha reductase enzyme). This medication, in a 0.5-mg per day dose, is marketed under the name Avodart in the USA and Avolve in Europe. In the treatment of prostate problems, dutasteride has produced breast tenderness and breast enlargement. It has also caused impotence and decreased sexual interest in a small number of men taking the drug.

In November 20, 2001 the FDA approved dutasteride 0.5-mg/day (Avodart) for the treatment of symptomatic benign prostatic hyperplasia (BPH). The phase III human trials, using the 0.5-mg dose, involved 2166 men at least 50 years of age with (BPH) diagnosed by history and physical examination, including enlarged prostate (≥ 30 cc) and BPH symptoms that were moderate or severe according to the American Urologic Association Symptom Index (AUA-SI).

Phase III human trial of dutasteride for hair growth were postponed indefinitely. Phase II clinical studies after 6 months treatment with dutasteride 0.05 mg to 2.5 mg showed an increase in hair count within a 1 inch diameter circle of 96 hairs with 0.5 mg/ day and 108 hairs with 2.5mg/ day. A six month course of finasteride 5mg/ day resulted in an increase in hair counts in a one inch circle of 72 hairs. There is a suggestion from the phase II clinical trials that hair counts may increase in the frontal area also.

Hair counts with finasteride 1mg showed a gain of 86 hairs in a one-inch circle at the end of one year. These hairs were significantly larger than the fine, miniaturized hair seen in balding, but it is not clear if they all assumed the full weight and diameter of the patient's original hair. As a comparison, hair transplantation can add significantly more density in a single session, and this number can be increased in subsequent sessions. In addition, transplanted hair has the full weight



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and diameter of the patient's original hair and, of course, is permanent.

The half life of dutasteride is 5 weeks at steady state. The average steady state concentration is 40ng/ml following 0.5 mg/day for one year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life dutasteride serum concentrations remain detectable (greater than 0.1ng/ml) for up to 4 to 6 months after discontinuation of treatment.

Due to the long half-life side effects may last much longer. Therefore, we recommend you take Propecia for 6 months to one year prior to starting dutasteride. If you tolerate Propecia well, you may consider switching to dutasteride at the end of your Propecia trial period. While higher dosages up to 2.5 mg of dutasteride have been shown to increase hair counts even greater than 0.5mg, this higher dosage has not been submitted to the FDA for their approval and no phase III human clinical trial at this dosage exist.

Dutasteride has not been studied in individuals under 18 years of age. No dose adjustment is necessary in the elderly. The effect of dutasteride on race has not been studied. The effect of renal impairment has not been studied but no dose adjustment is anticipated. The effect in hepatic impairment has not been studied, but it is anticipated that since dutasteride is metabolized by the liver that dose adjustment would be necessary in patients with hepatic impairment.

Drug Interactions

Dutasteride is metabolized by human cytochrome P450 isoenzyme CYP3A4. No clinical drug interaction studies have been performed to evaluate the impact of CYP3A4 enzyme inhibitors on dutasteride pharmacokinetics. However, based on the in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin. Clinical drug interaction studies have shown no pharmacologic or pharmacokinetic interactions between dutasteride and tamsulosin, terazosin, warfarin, and cholestyramine. Caution should be used in those with liver disease, who chronically take CYP3A4 enzyme inhibitors.

Effects on PSA and Prostate Cancer Detection

Digital Rectal examinations, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with dutasteride and periodically afterward. Dutasteride reduces PSA (prostatic specific antigen), which is a blood test marker for prostate cancer, by approximately 20% following a one month of therapy, 40% following 3 months of treatment, and 50% following 6 and 12 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs in a man taking dutasteride a new baseline PSA concentration should be established after 3 to 6 month of treatment, and this new value should be used to assess potentially cancer related changes of PSA. To interpret an isolated PSA value in a man treated with dutasteride for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.



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Patients are instructed to read the Information for Patient leaflet before starting therapy with dutasteride and to reread it upon renewal of dutasteride for new information regarding dutasteride.

Contraindications

Avodart is contraindicated in women and children. Avodart is contraindicated for patients with a known hypersensitivity to dutasteride, other 5-alpha-reductase inhibitors, or any component of its preparation.

Blood Donation

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

Sexual Dysfunction

Although uncommon, there can be side effects of dutasteride at the 0.5 mg/day dose. These include decreased libido (1.8%), impotence (1.3%), and decreased volume of ejaculate (1.2%). It is important to note that there was a small incidence of these problems in the control group as well. Altogether, 3.8% of men taking finasteride 1mg experienced some form of sexual dysfunction versus 2.1% in men treated with placebo (a sugar pill).

Most reported cases of sexual dysfunction occurred soon after the medication was begun, but there have been reports of sexual dysfunction that have occurred at later time points. The sexual side effects were reversible in all men who discontinued therapy and in 58% of those who chose to continue treatment. When the medication was stopped, side effects generally went away within weeks, but occasionally took longer.

If sexual side effects occur, they generally begin well before finasteride has had a chance to have visible effects on hair growth. Therefore, men who experience side effects can discontinue the Propecia at this time without the risk of hair loss due to stopping the medication. It is important to remember that when finasteride (or minoxidil) is discontinued, you only lose the hair that was gained or preserved by the medication, not more. In effect, you return to the level of balding that you would have been if you had never used the drugs in the first place.

Reproductive Function

Semen characteristics were evaluated at 3 time points in normal volunteers aged 18 to 52 (n=26) over a 52 week period. No clinically meaningful changes in sperm concentration, sperm motility, or sperm morphology were noted. A 0.8 ml (25%) decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed at 52 weeks. These parameters



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remained within the normal limits.

CNS Toxicity

At 425 and 315 fold the expected clinical drug some rats and dogs exhibited signs of non-specific, reversible, centrally-mediated toxicity without associated histopathological changes.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

At 290-fold the expected clinical exposure female B6C3F1 mice exhibited an increase in benign hepatocellular adenomas. At 135-fold the expected clinical exposure Han Wistar rats exhibited an increased incidence of Leydig cell adenomas in the testes. Leydig cell hyperplasia was evident in male rats at 52-fold and 135-fold the expected clinical exposure. A positive correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5 alpha-reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5 alpha-reductase inhibitions. At tumorigenic doses in rats luteinizing hormone levels were increased by 167%.

There is not evidence that dutasteride mutagenic or exhibits signs of genotoxicity.

There were dose and time dependent decreases in fertility, epididymal sperm counts, reduced weights of the epididymis, prostate, and seminal vesicles and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses and sperm counts were normal at the end of a 14-week recovery period.

Gynecomastia

Adverse reactions related to the breast, including breast tenderness or enlargement (gynecomastia), occurred in 1% of men taking dutasteride and <1% of patients taking placebo. The risk of gynecomastia increases from 1% the first year to 2% during the second year of treatment.

In patients on the 5-mg dose (Proscar), the time of onset of breast enlargement ranged from two weeks to 2½ years. In these patients, 80% showed partial or complete resolution when the drug was stopped, and 20% experienced no change.

The mechanism of breast enlargement (gynecomastia) in patients taking finasteride may be due to its ability to block the conversion of testosterone to DHT. This, in turn, may cause more



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testosterone to be converted to estrogen, with estrogen then stimulating breast tissue. There have been a few cases of breast cancer in patients on the 5-mg dose, but a causative relationship with finasteride has not been established.

Other Adverse Effects

The side affects of dutasteride are summarized below.

Adverse Event	Placebo (n = 2158)	Avodart (n = 2166)
Impotence	59 (3%)	117 (5%)
Decreased Libido	40 (2%)	74 (3%)
Ejaculation Disorders	14 (<1%)	40 (2%)
Gynecomastia	10 (<1%)	29 (1%)

The side affect profile for one group that took dutasteride 0.5mg for 24 months was consistent with that observed after 12 months of treatment. The incidence of onset of drug related events was lower during the second year of treatment compared with the first year of treatment, with the exception of Gynecomastia (onset 1% during the first year and 2% during the second year).

Effects on PSA

Finasteride causes an approximate 1/3 decrease in serum PSA (prostate specific antigen) in normal men (from 0.78ng/ml to 0.52 ng/ml). It may also blunt the rise of PSA levels in patients with prostate enlargement and in patients who have developed prostate cancer.

Since PSA is used as a screening test for the development of prostate cancer (the most common type of non-skin cancer in men), there is a concern that the use of Propecia may interfere with the detection of this disease. It is important that your personal physician is aware that you are taking finasteride so that he can take into account any effects that finasteride may have on your PSA. It is possible that the long-term use of Propecia may actually decrease the incidence of prostate



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disease, but this has not yet been confirmed in scientific studies.

Teratogenicity in Females

Dutasteride is contraindicated for use in women of childbearing age since birth defects in males can occur if significant amounts of the drug are absorbed into the body during fetal development. It is advised that the soft Gelatin Capsules not be handled by pregnant women out of concern that they may cause harm to the male fetus. However, to our knowledge, there has not been a single reported case of birth defects caused by women handling broken or crushed finasteride tablets or dutasteride soft gelatin capsules. The concern of handling crushed tablets or gelatin capsules seems to revolve around the FDA policy of assuming maximal possible absorption of the full concentration of the medication during any contact.

There is no evidence that exposure of dutasteride to pregnant women through semen is a risk to the human fetus, but for those patients who wish to limit any potential contact of dutasteride to their partner during pregnancy, a condom can be worn once conception has occurred. Your safest solution is to delay conception until you have ceased taking dutasteride for 6 months or to use a condom for 6 months after cessation of dutasteride should your significant other become pregnant.

Use in Post-Menopausal Women

There has been no research of dutasteride in post-menopausal women. Finasteride (Propecia) has no beneficial effects in post-menopausal women. Therefore, there is no reason to suspect dutasteride will be beneficial to post-menopausal women either. The safety profile for the use of dutasteride in post-menopausal women has not been established.

Long-Term Benefits and Risks

The effects of dutasteride are confined to areas of the scalp that are thinning, but where there is still some hair present. It does not seem to grow hair in areas that are completely bald. Therefore, the major benefit of dutasteride seems to be in its ability to slow down or halt hair loss, or regrow hair in parts of the scalp, which are thin. The long-term ability of dutasteride to maintain one's hair is unknown..

The benefits of dutasteride will most likely stop if the medication is discontinued. Over the 6 to 12 months following discontinuation, the hair loss pattern will most likely return to the state that it would have been if the medication had never been used.

It is important to understand that this medication is not FDA approved. The long term side affects of this medication are not known. Its long term affects on fertility are not known. Only long-term experience with the medication will be able to determine all of its potential effects. Dutasteride is a very long acting medication, which means it is slowly eliminated from the body. Its side affects may persist over the long duration of time it may take to eliminate this medication.



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The side effects could last 4 to 6 months or longer while the medication is being eliminated. We know from those genetically deficient in Type I 5 alpha-reductase that there are no long term significant abnormalities, but we do not know how a long term competitive inhibition of both Type I and Type II 5 alpha reductase will impact the human body.

Dutasteride and Hair Transplantation

Avodart (dutasteride) may be shown to be a useful adjunct to surgical hair restoration for a number of reasons.

- Avodart may work best in the younger patient who may not yet be a candidate for hair transplantation.
- Unlike Propecia, Avodart is probably effective in the front part of the scalp, the area where surgical hair restoration can offer the greatest cosmetic improvement. The additive effects of surgical hair restoration and Avodart may be complimentary.
- Propecia can regrow, or stabilize hair loss, in the back part of the scalp where hair transplantation may not always be indicated. Avodart may likely perform similar results.
- If Avodart is shown to be safe and effective in the long-term, it will allow the hair restoration surgeon the ability of creating more density in the cosmetically most important areas (such as the front part of the scalp), since keeping reserves for future hair loss in other areas will be less of a concern.

Patient Monitoring

Men age 40 or over, should consult their regular physician or urologist before beginning Avodart (dutasteride) or Propecia (finasteride 1mg). For those age 40, or over, and are black and/or have a family history of prostate disease, it is recommended that you be evaluated yearly. If you have no family history of prostate problems and are not black, yearly prostate examinations should begin at age 50. This may include a rectal examination, a baseline PSA, and other tests that your examining physician feels are appropriate. You should have another PSA baseline test following 3 to 6 months of treatment with dutasteride or Propecia.

Please note that these are general guidelines recommended for all men of the appropriate age, regardless of whether or not they use dutasteride or finasteride. Specific recommendations for each patient should be based upon the judgment of his own physician.

Prescriptions

Your first prescription for dutasteride will be for a 6-month supply. Renewals will be for one year. If you desire to have an IHTI physician prescribe this medication, there will be an \$85 fee for the initial prescription or renewals. You are encouraged to return to our office for follow-up. At each visit, you will be examined and any new information regarding dutasteride and/or other therapies will be communicated to you. You will be responsible for obtaining urology evaluations if appropriate. If you experience any problems or adverse reactions while taking dutasteride, please contact us and/or your prescribing physician.



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Last Name, First

Signature Date