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July 20, 2016

VIA ECF FILING
The Honorable Judge Peggy Kuo
Magistrate Judge
United States District Court
Eastern District of New York
225 Cadman Plaza East
Brooklyn, NY 11201

Re: In re: Propecia (Finasteride) Products Liab. Litig. MDL 2331 Plaintiffs' Motion to Amend PPO No. 10 and Extend Discovery Deadline to Allow for Requests for Admission.

Dear Magistrate Judge Kuo,

I write on behalf of the Plaintiffs Executive Committee ("PEC") in the above-captioned matter, and in accordance with the briefing scheduled outlined by your Honor during the July 6, 2016 Case Management Conference. The intention of this letter is to request that this Court extend the discovery deadline, as outlined in the second amended PPO No. 10, so that Plaintiffs may propound general liability requests for admission. Specifically, the PEC requests PPO No. 10 be amended to include a deadline to serve Requests for Admission on or before October 1, 2016.

INTRODUCTION

Since 2013, the parties have participated in discovery. General merits discovery was scheduled to be completed no later than June 24, 2016. *See Second Amended Discovery & Trial Plan Procedure and Practice Order No. 10*, (Dkt. No. 295). However, despite the Court's deadline and the parties' best efforts, key corporate depositions were not conducted prior to the general merits discovery deadline or were not conducted within thirty days of the discovery deadline. In addition, more than 60,000 pages of documents were produced at the absolute conclusion of the general merits discovery deadline – with an additional 20,000 pages of documents being produced after the close of general merits discovery.

As a result, the PEC could not have propounded requests for admission thirty days prior to June 24, 2016, as key facts in this litigation were not yet known by Plaintiffs. Allowing the PEC to propound requests for admission after June 24, 2016 is neither prejudicial to Defendants, Merck & Co., Inc. and Merck Sharp & Dohme Corp., ("Merck"), nor will it result in any delay in the litigation or the Trial Plan. As such, the PEC respectfully requests the Court amend PPO. No. 10

to extend the discovery deadline to allow the PEC to serve requests for admission on or before October 1, 2016.

FACTS

The Second Amended PPO No. 10 required general merits discovery be completed on or before June 24, 2016. Due to scheduling issues of both Counsel and the witnesses, key corporate witnesses' depositions were either not conducted within thirty days of the discovery deadline or occurred after the deadline. By way of example, the PEC took Charlotte Merritt's deposition on May 19, 2016. Merritt was a lead in regulatory and global affairs at Merck from 1990 to 2013. The PEC took Paul Howes's deposition on June 7, 2016—17 days prior to the close of discovery. Paul Howes served as Vice President of Sales and Marketing, Specialty Products at Merck from 1998 to 2001. His role was critical to understanding Merck's marketing scheme at the time it launched Propecia, and in particular Merck's intention to treat Propecia as a potential "Blockbuster" drug. Similarly, due to scheduling issues, the PEC took Dr. Keith Kaufman's deposition on July 13, 2016—*i.e*, nearly three weeks after the general merits discovery deadline. Dr. Kaufman served as Director of Clinical Research at Merck Research Laboratories from 1997 to 2008 and as Vice President of Clinical Research at Merck Research Laboratories from 2008 to present. As the Director of Clinical Research, his testimony was clearly relevant to Merck's clinical trials, post marketing activity and alterations to Merck's label in both Europe and the United States.

The delay was not limited exclusively to conclusions of key depositions. Specifically, on June 24, 2016—the very last day of general merits discovery—Merck served approximately 66,727 pages of documents. This production consisted of board of directors minutes, labeling, and non-custodial hard copy files. On July 7, 2016, after the close of general merits discovery, Merck produced an additional 20,890 pages of documents. This production consisted of regulatory files concerning Sweden and the United Kingdom. Given the dates of production, Plaintiffs were unable to review these documents prior to the conclusion of general merits discovery; let alone use them in relevant depositions. It was not until these productions, as well as the depositions of key corporate witnesses, that the PEC was fully able to comprehend key issues in this litigation that would be addressed in the requests for admission.

ARGUMENT

A. This Court has Broad Discretion to Manage its Docket and Scheduling of the Litigation is Oversees.

It is axiomatic that all Courts possess broad discretion to manage their dockets and the schedules of the litigations they oversee. *See McKay v. Triborough Bridge and Tunnel Auth., et al*., No. 05 Civ. 8936, 2007 WL 3275918, at *1 (S.D.N.Y. Nov. 5, 2007) ("A district court has broad discretion to direct and manage the pretrial discovery process."); *Wills v. Amerada Hess Corp*., 379 F.3d 32, 41 (2d Cir.2004); and *Syracuse University v. Otis Elevator Co., No. 5:09–CV–0172, 2010 WL 2680230*, at *2-3 (N.D.N.Y. July 1, 2010). *See, e.g., Com Tech Assocs. v. Computer Assoc. Int'l*, 753 F.Supp. 1078, 1079 (E.D.N.Y.1990), *aff'd*, 938 F.2d 1574 (2d Cir.1991) (where the court determined that magistrate judges have broad discretion in resolving nondispositive

matters regarding discovery orders); and *United States v. Ferguson*, 246 F.R.D. 107, 126-27 (D.Conn.2007) (finding "[a] district court has broad discretion to deny a request to postpone a trial to accommodate defense counsel's schedules."). Similarly, courts routinely extend deadlines in schedules particularly where the extension does not prejudice the opposing side or extend the trial date. *See* Fed.R.Civ.P. 16(b)(4) (purporting that "[a] schedule may be modified only for good cause and with the judge's consent."). *See also, Arnold v. Krause, Inc.*, 232 F.R.D. 58, 65 (W.D.N.Y.2004) (finding that good cause is required to modify a scheduling order to extend deadlines), *aff'd*, 233 F.R.D. 126 (W.D.N.Y.2005); and *Ritchie Risk-Linked Strategies Trading (Ireland), Ltd. v. Coventry First LLC*, 280 F.R.D. 147, 161-162 (S.D.N.Y.2012) (allowing for a reasonable continuance of discovery). Here, the proposed extension does not seek to amend the trial date nor does it result in prejudice to Merck. Each will be discussed in turn.

On its face, the amendment does not implicate the trial date. Specifically, the amendment would require the requests for admission be served on or before October 1, 2016—nearly twelve months prior to the proposed trial date. Equally important, the extension will not prejudice Merck. For example, the current schedule requires completion of case-specific discovery by September 15, 2016. The schedule further dictates that the Parties propose their trial-picks by September 22, 2016. Finally, Plaintiffs' initial expert reports are due December 15, 2016 with Merck's opposition reports due in January, 2017. In other words, between September 22, 2016 and December 15, 2016 (nearly ninety days) there is a relative lull in the schedule that affords the Parties ample time to propound *and complete* the requests for admission. In short, there is simply no prejudice.

Equally important, the requests for admission will not be used to merely engage in busy work. Instead, the requests for admission will be used to evidence key components of Plaintiffs' claims for negligent failure to warn and punitive damages. Specifically, discovery to date revealed credible facts evidencing Merck was aware of the following: 1) persistent ongoing sexual dysfunction stemming from both post-marketing reports *and* the clinical trials themselves; 2) the existence of a safety-signal identifying a causal association between Propecia and ongoing sexual dysfunction; 3) flaws in Merck's regulatory conduct; and 4) motive—*i.e.*, that Merck intentionally ignored signs of harm so as to increase sales. By way of example only:

- Dr. Elizabeth Round conceded the label was deficient in that it failed to identify a temporal nexus from the time of discontinuation to the time of resolution (*See Deposition of Elizabeth Round* at 191-205 attached hereto as Exhibit A);

- Charlotte Merritt, the person at Merck who oversaw regulatory activity related to Propecia conceded that Merck changed the label from: "Resolution occurred in ***all*** men who discontinuation therapy with Propecia . . ." to "Resolution occurred in men who discontinued therapy with Propecia . . ." *Cf. Propecia Label 2001* (emphasis supplied) attached as Exhibit B with *Propecia Label 2002* attached as Exhibit C. She further testified Merck eliminated the word "all" due to evidence *from the clinical trials* of persistent ongoing erectile dysfunction following discontinuation of use. She

also testified that Merck made no others changes to the label at that time. *See Deposition of Charlotte Merritt* at 109-118 attached hereto as Exhibit D.

- Dr. Cynthia Silber, the person at Merck who oversaw post-marketing safety and surveillance, conceded that Merck identified a "safety-signal" related to persistent ongoing erectile dysfunction as early as 2006, but did not amend the label until 2012. *See Deposition of Cynthia Silber* at 43-51 attached hereto as Exhibit E. The relevance of this is that a safety-signal is evidence of a causal association between a drug and a particular risk (in this case persistent erectile dysfunction).

- Paul Howes, the head of marketing for Merck related to Propecia from 1998 through 2002, conceded that between 1997 and 2002 Merck was on track to lose patent protection for several key drugs resulting in the potential loss of billions of dollars of revenue (*see Deposition of Paul Howes* at 15-38 attached as Exhibit F); that Propecia was distributed, in part, to plug the gap in lost revenue (*Id.* at 35-38); and that Merck was keenly aware that references to sexual side effects—particularly persistent to permanent side effects—would have a devastating impact on sales (*Id.* at 91-99).

The purpose of requests for admission is to streamline evidentiary disputes at trial and during summary adjudication. Specifically, the purpose of requests for admission is to narrow the issues of the case, *e.g.*, "weeding out of the facts" in an effort to reduce trial effort and promote litigation efficiency. *See Booth Oil Site Admin. Group v. Safety–Kleen Corp*., 194 F.R.D. 76, 79 (W.D.N.Y.2000); and *In re Carousel Candy Co.*, 38 B.R. 927, 930 (Bankr.E.D.N.Y.1984) (noting the purpose of requests for admission is to "narrow and define issues for trial"). *See also, United Coal Companies v. Powell Const*. Co., 839 F.2d 958, 967 (3d Cir.1988); *Dubin v. E.F. Hutton Group, Inc*., 125 F.R.D. 372, 375 (S.D.N.Y.1989) (citing 8 C. Wright & A. Miller, Federal Practice & Procedure, § 2253 (1970)); and *Webb v. Westinghouse Electric Corp*., 81 F.R.D. 431, 436 (D.C.Pa.1978). Here, the facts set forth above are drawn directly from testimony elicited during depositions. Use of requests for admission will assist both the Court and trier of fact in that they will streamline admissions made by Merck employees throughout discovery. As such, allowing the PEC to serve requests for admission will not only assist the trier of fact, but also streamline the trial process to "weed out" those facts Merck admitted at during discovery.

B. The PEC Requests a Nominal Extension to the Discovery Schedule out of an Abundance of Caution and so as to Avoid Any Ambiguity.

Rule 36 of the Federal Rules of Civil Procedure governs requests for admissions, and provides that a party may serve a request for admission relating to the "application of law to fact." The Advisory Committee Note to the 1970 amendments of Rule 36(a) further explains that a request to admit may concern "matters involving 'mixed law and fact.'" *See Abbott v U.S.*, 117 F.R.D. 92, 93 (N.D.N.Y. 1997). *See generally, Walsh v. Connecticut Mutual Life Ins. Co*., 26 F. Supp. 566 (E.D.N.Y. 1939); and *Nekrasoff v. U. S. Rubber Co*., 27 F. Supp. 953 (S.D.N.Y. 1939). Generally, "Requests for admissions are not a general discovery device." *Hurt v. Coyne*

Cylinder Co., 124 F.R.D. 614, 615 (W.D. Tenn. 1989); *Misco, Inc. v. United States Steel Corp.*, 784 F.2d 198, 205 (6th Cir.1986); and 8 C. Wright and A. Miller, Federal Practice and Procedure § 2253, at 706 (1970). In fact, the Southern District of New York unequivocally concluded, "Requests for admissions are not a discovery device much like interrogatories, demands for documents, or depositions, nor are they to be considered substitutions for them." *See T. Rowe Price Small–Cap Fund, Inc. v. Oppenheimer*, 174 F.R.D. 38, 42 (S.D.N.Y.1997). *See also*, James Wm. Moore., Moore's Federal Practice ¶ 36:02 (3d ed.2002). In other words, requests for admission are typically not viewed as "discovery" because they do not elicit new information—instead, they merely confirm information obtained *during discovery.*

Given requests for admission are not considered a form of discovery, as their intent is not to obtain new information, it is also generally understood that requests for admission are therefore not governed – and need not be propounded or answered – by discovery deadlines. *See In re Carousel Candy Co.*, 38 B.R. 927, 930 (Bankr.E.D.N.Y.1984) (where requests for admission are not considered discovery devices, as their purpose is not necessarily to obtain new information). *See generally, Diederich v. Dep't of the Army*, 132 F.R.D. 614 (S.D.N.Y.1990) (where the court concluded that requests for admissions were not discovery devices and do not need to be propounded or answered before the close of discovery). The implication from these cases suggests that propounding requests for admission falls beyond deadlines for the close of discovery. Nonetheless, this view is not universally accepted. Specifically, some courts within the Second Circuit—and in particular in New York—conclude that requests for admission must be proffered in time to be completed *prior* to the close of discovery. *See Greenfield v. Mem'l Sloan Kettering Hosp.*, No. 95 Civ. 7658, 2000 WL 351395, at *5 (S.D.N.Y. Apr. 5, 2000) ("There is apparently no clearly defined precedent [on the question of whether requests for admissions are governed by discovery deadlines] from the Second Circuit[.]"). As a result, and out of an abundance of caution, the PEC seeks to impose a precise deadline to complete requests for admission *as it relates to general merits discovery.*

As with the case law cited above, the PEC does not wish to utilize requests for admission to obtain any new information. Instead, the PEC intends to use the requests for admission to "narrow and define" the issues for trial. Given the PEC was unable to propound requests for admission within thirty days of the close of discovery due to the fact key depositions took place so near (or after) the close of discovery, and Merck produced more than 60,000 pages of discovery *on the last day* of general merits discovery – with an additional 20,000 pages of documents being produced after the close of discovery, it was practically impossible to serve requests for admission prior to the close of discovery. As such, the Court should amend PPO No. 10 to allow Plaintiffs to propound requests for admission past the general merits discovery deadline. Allowing the requests for admission will not delay the litigation or discovery, nor will it prejudice any party. The PEC makes this request out of an abundance of caution given the conflict between the case law in this Circuit governing the timing of serving requests for admission. Accordingly, refusing to allow the PEC to serve requests for admission not only prejudices Plaintiffs, but also will cause needless delay at trial. As such, the PEC respectfully requests the Court's permission to extend the schedule and allow requests for admission by October 1, 2016.

CONCLUSION

The PEC now asks the Court to amend PPO No. 10 so that the PEC may serve upon Merck Requests for Admission beyond the conclusion of general merits discovery. While the PEC believes the case law and precedent to rule clearly in their favor, out of an abundance of caution, the PEC seeks the Court's permission and clarification with regard to either party propounding and answering requests for admission after the close of general merits discovery.

Date: July 20, 2016

Respectfully submitted,

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Plaintiffs' Executive Committee

Cc: All Counsel registered with ECF.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

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IN RE:	:	Master File No.:
PROPECIA (FINASTERIDE)	:	1:12-md-02331-JG-
PRODUCTS LIABILITY	:	VVP
LITIGATION	:	MDL No. 2331
This Document Relates To:	:	Honorable John Gleeson
	:	Magistrate Judge
ALL CASES	:	Viktor Pohorelsky

- - -

DECEMBER 17, 2015

- - -

Videotape deposition of ELIZABETH ROUND, M.D., taken pursuant to notice, was held at the law offices of Venable LLP, 1270 Avenue of the Americas, 24th Floor, New York, New York 10020, beginning at 9:06 a.m., on the above date, before Amanda Dee Maslynsky-Miller, a Certified Realtime Reporter and Notary Public in and for the State of New York.

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deps@golkow.com

BY MR. BECKER:

Q. So I have in front of you there, Doctor, Exhibit-56.

Do you see that there?

A. Yes.

Q. Okay. This also appeared in your custodial file.

Do you recall reviewing this document or reading this article?

A. I recall the article.

Q. Okay. It's an article from Dr. Irwig, of the George Washington University, entitled, "Persistent Sexual Side Effects for Finasteride For Male Pattern Hair Loss."

Did I read that correctly?

A. Yes.

Q. And it appears in the Journal of Sexual -- Sex Medicine, correct?

MR. MORROW: Objection.

THE WITNESS: Yes.

BY MR. BECKER:

Q. The article is dated 2011.

Do you see that there?

A. Yes.

Q. I want to go through just some of his results.

All right. You recall reading this article at the time you received it?

A. I read it at the time I received it, yes.

Q. And in connection with that, you had an understanding that Dr. Irwig had evaluated a cohort of men who believed that they had persistent ongoing sexual dysfunction following discontinuation of use, correct?

A. Yes.

Q. And he reported, after that review, that 94 percent of the subjects developed low libido, correct?

MR. MORROW: Objection.

THE WITNESS: That's what the statement says here.

BY MR. BECKER:

Q. And 92 percent developed

erectile dysfunction.

Do you see that?

A. Yes.

MR. MORROW: Form.

BY MR. BECKER:

Q. 92 developed decreased arousal?

MR. MORROW: Object to the form.

THE WITNESS: Yes.

BY MR. BECKER:

Q. And 69 percent developed problems with orgasms.

Do you see that there?

MR. MORROW: Object to the form.

THE WITNESS: Yes.

BY MR. BECKER:

Q. Do you have any evidence, as you sit here today, that that data was, in fact, inaccurate?

MR. MORROW: Objection.

This is.

THE WITNESS: This is a

selected group of patients with sexual AEs following finasteride.

BY MR. BECKER:

Q. Right. I mean, it's men who are saying, I continue to have adverse events -- I continue to have sexual dysfunction following the time I stopped taking PROPECIA®, right?

A. Yes.

MR. MORROW: Objection.

BY MR. BECKER:

Q. And they're reporting these are their symptoms, true?

A. Yes.

Q. What, if anything, did Merck do with this data?

MR. MORROW: Object to the form.

THE WITNESS: We reviewed the paper.

BY MR. BECKER:

Q. And based upon your review, what did you do?

A. I don't recall that we took

any action, if that's what you're asking.

Q. He reports that, The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months from the time of finasteride cessation to the interview date.

Do you see that?

A. I do.

Q. Would 40 months constitute persistent ongoing sexual dysfunction?

MR. MORROW: Objection.

THE WITNESS: I don't have a definition for persistent.

BY MR. BECKER:

Q. So if a label talks about symptoms being resolved upon discontinuation of use, don't you think it would be fair to tell doctors and patients what the temporal nexus was between the time the person discontinued the use and the date when the symptoms actually went away?

MR. MORROW: Objection.

THE WITNESS: Well, we didn't. We stated they were resolved upon discontinuation.

BY MR. BECKER:

Q. But let's assume for argument's sake that these men's symptoms resolved at 40 months. Isn't there a difference between a label that says your symptoms will resolve 40 months after you discontinue use versus your symptoms will ultimately resolve?

Isn't there a fundamental difference between those two statements?

MR. MORROW: Object to the form.

THE WITNESS: There is a difference.

BY MR. BECKER:

Q. Is Merck putting patient safety first when it refuses to identify the temporal connection between discontinuation of drugs and how long it takes for those symptoms to actually resolve?

MR. MORROW: Object to the form.

THE WITNESS: No. The persistence of sexual AEs has been added to the label based on postmarketing. We've also established that postmarketing data is limited. And this author himself cites the limitations of this study; the post hoc approach, selection bias, record bias, no serum hormone level.

MR. BECKER: Objection, nonresponsive. Move to strike everything after "no."

MR. MORROW: Objection.

BY MR. BECKER:

Q. My question is, Doctor, if we can agree that time from discontinuation to resolution is important, shouldn't you tell patients what that time is?

MR. MORROW: Object to the form. That's a different

question.

THE WITNESS: It would appear to be very variable for each of these patients.

BY MR. BECKER:

Q. That didn't answer my question.

You either should or shouldn't have to tell them what the time is.

What's your view?

MR. MORROW: Objection.

THE WITNESS: I don't think there's a need to tell them the time.

BY MR. BECKER:

Q. So in Merck's view, if the time to resolution was three and-a-half years, it would be okay to withhold that information from patients?

MR. MORROW: Object to the form. Mischaracterizes the testimony.

You may answer.

THE WITNESS: No, that shouldn't be withheld from the patient.

BY MR. BECKER:

Q. So at what point in time does persistence become -- at what point in time do you believe Merck should alert patients that it takes to resolve these symptoms after discontinuation?

MR. MORROW: Object to the form.

MR. BECKER: Let me start over because I agree with his objection on that one.

BY MR. BECKER:

Q. It's fair there's no -- there's no indication in the label that symptoms will resolve after a given amount of time has passed, right?

A. Right.

Q. All the label says is that stop taking the drug and the symptoms go away?

A. Uh-huh.

Q. Yes?
A. Yes. In the clinical trials --
MR. MORROW: Objection.
THE WITNESS: -- yes.
BY MR. BECKER:
Q. Isn't it a fair inference from that, that the symptoms resolve quickly after you discontinue use?
MR. MORROW: Objection. Speculation.
THE WITNESS: Based on the clinical trials, I don't believe it was a long time.
BY MR. BECKER:
Q. That wasn't my question.
My question was, wasn't the inference that Merck was making was that symptoms would quickly resolve upon discontinuation of use?
MR. MORROW: Object to the form.
THE WITNESS: I don't know that the argument was quickly

resolve. We just said that they would -- they resolved on discontinuation, what we saw in the clinical trials.

BY MR. BECKER:

Q. Can we -- would you agree with me that the longer it takes to have these symptoms resolve after discontinuation of use, the more obligation Merck has to alert patients of that -- of that issue?

MR. MORROW: Object to the form.

THE WITNESS: We now have reports in the adverse experiences section that talk about persistence. We don't put a qualifying -- a qualifying time period on that.

MR. BECKER: Objection. Hold on. Nonresponsive. Move to strike.

BY MR. BECKER:

Q. Let me see if I can do it

this way, Doctor.

Would you agree that if in some men these symptoms occurred six months after discontinuation of use, that Merck would have an obligation to report that in the label?

MR. MORROW: Objection.

THE WITNESS: Do you mean that these events had a new onset six months after?

BY MR. BECKER:

Q. No, no. I'm asking you, Merck does not dispute the fact that sexual -- adverse sexual events can occur while on a drug; you don't dispute that, do you?

A. No.

Q. Merck takes the position that at some point following discontinuation of use, those symptoms go away, right?

A. As observed in the trials, yes.

Q. What I'm trying to get at

is, how long after discontinuation of use should Merck tell patients and doctors those symptoms take to resolve?

Do you understand my question?

A. I do understand the question.

MR. MORROW: Objection.

You can answer.

BY MR. BECKER:

Q. And my question is, would you agree that if the symptoms did not resolve for a month, that Merck should alert patients who take the drug that it may take up to a month for their sexual dysfunction -- for their sexual function to return?

MR. MORROW: Objection.

BY MR. BECKER:

Q. Should you tell patients that?

MR. MORROW: Objection.

BY MR. BECKER:

Q. Should you tell patients

that?

MR. MORROW: Objection.

THE WITNESS: If we had that information, yes.

BY MR. BECKER:

Q. Okay. Now, you have a worldwide adverse event database, right?

A. Yes.

Q. And you had clinical trials, right?

A. Yes.

Q. And in those clinical trials, the data reported resolution after discontinuation of use for some patients, right?

A. Yes, yes.

Q. And sometimes that resolution took several hundred days or up to a year, right?

MR. MORROW: Objection.

THE WITNESS: I don't know that.

BY MR. BECKER:

Q. If the data demonstrates

that resolution took a long time following discontinuation of use, shouldn't you have told patients and doctors that?

MR. MORROW: Object to the form.

THE WITNESS: I don't remember the data on how long it took to -- for resolution.

BY MR. BECKER:

Q. That wasn't my question, though.

A. I understand.

Q. So I'd like an answer to my question.

MR. MORROW: Same objection.

THE WITNESS: If -- it may have been useful to put that in.

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(Whereupon, Exhibit-57, 4/6/11 E-mail to Cynthia Silber from Christine Alberts, Bates MRKP0001390080-81, was marked for identification.)

PROPECIA®

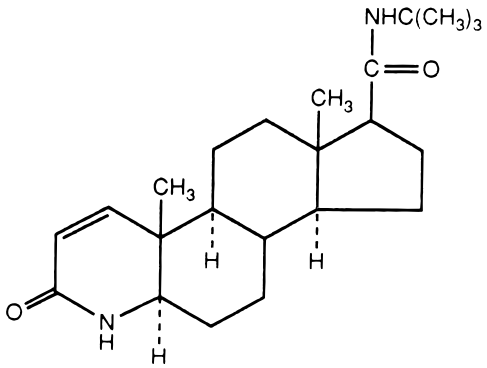
(Finasteride)

Tablets, 1 mg

DESCRIPTION

PROPECIA* (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

PROPECIA tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

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* Registered trademark of MERCK & CO., INC.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme (IC_{50}=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone, indicating that the hypothalamic-pituitary-testicular axis was not affected. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

Pharmacokinetics

Following an oral dose of ^{14}C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possessed no more than 20% of the 5α-reductase inhibitory activity of finasteride.

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of AUC relative to a 5-mg intravenous dose infused over 60 minutes. Following intravenous infusion, mean plasma clearance was 165 mL/min (range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44-96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20-154 ng•hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng per day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys (see PRECAUTIONS, *Pregnancy*).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance, and a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 mL/min), the values for AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). Furthermore, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Clinical Studies

Studies in Men

The efficacy of PROPECIA was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies (controlled phase and extensions), all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®** Shampoo).

There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. In addition, information was collected regarding sexual function (based on a self-administered questionaire) and non-scalp body hair growth. The three studies were conducted in 1,879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1,553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

Studies in Men with Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial and extension periods (up to 24 months) and 60 men receiving placebo for the same periods. In addition, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the 12-month extension period, and 543 men who received placebo for the initial 12 months followed by PROPECIA in the 12-month extension period (See Figure below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, PROPECIA [n=679 evaluable men] vs placebo [n=672 evaluable men]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking PROPECIA (n=433 evaluable men) for up to 24 months, while the placebo group (n=47 evaluable men) continued to show progressive hair loss. At 24 months, this resulted in a 138-hair difference between treatment groups ($p<0.001$) within the same area. Patients who switched from placebo to PROPECIA (n=426 evaluable men) at the end of the initial 12 months had an increase in hair count at 24 months. A change of treatment from PROPECIA to placebo (n=48 evaluable men) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months. See figure below for combined study results.

At 12 months, 14% of men treated with PROPECIA had hair loss (defined as any decrease in hair count from baseline) compared with 58% of men in the placebo group. In men treated for up to 24 months, 17% of those treated with PROPECIA demonstrated hair loss compared with 72% of those in the placebo group.

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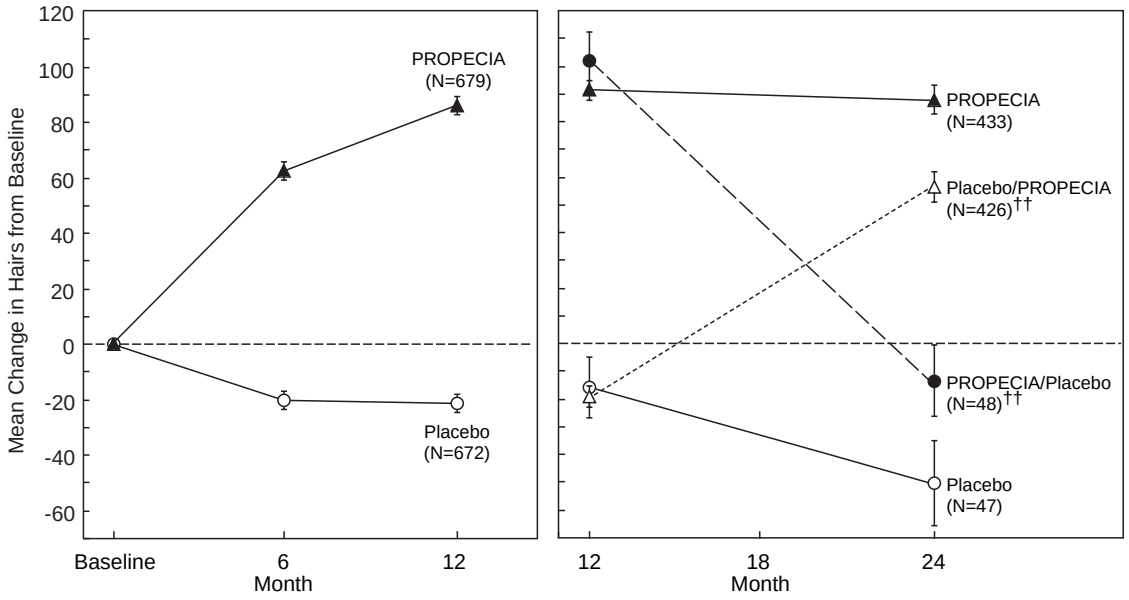
Effect on Hair Count†

Number of Hairs in a 1-Inch Diameter Circle
Mean Change ± 1 S.E.



† Pooled data from vertex hair loss studies (mean baseline hair count = 876)

†† At the end of initial 12-month period, treatment switched from PROPECIA to placebo (— — — — PROPECIA/Placebo) or from placebo to PROPECIA (---------- Placebo/PROPECIA).

Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with PROPECIA. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with continued improvement over 24 months.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with PROPECIA compared with placebo as early as 3 months ($p<0.001$). At 12 months, the investigators rated 65% of men treated with PROPECIA as having increased hair growth compared with 37% in the placebo group. At 24 months, the investigators rated 80% of men treated with PROPECIA as having increased hair growth compared with 47% of men treated with placebo.

Standardized photographs of the head were assessed in a blinded fashion, at the beginning of the study and at 6, 12, 18 and 24 months. An independent panel rated increases or decreases in scalp hair on the same 7-point scale as the investigator assessment. At 12 months, 48% of men treated with PROPECIA had an increase as compared with 7% of men treated with placebo. At 24 months, an increase in hair growth was demonstrated in 66% of men treated with PROPECIA compared with 7% of men treated with placebo. Based on this assessment, continued treatment with PROPECIA resulted in further improvement. These results were observed in the context of no further increase in hair count between month 12 and month 24.

Other Results in Vertex Baldness Studies

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. PROPECIA did not appear to affect non-scalp body hair.

Study in Men with Hair Loss in the Anterior Mid-Scalp Area

A third study of 12-month duration, designed to assess the efficacy of PROPECIA in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings

based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Summary of Clinical Studies in Men

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with PROPECIA or placebo received a tar-based shampoo (Neutrogena T/Gel®** Shampoo). Clinical improvement was seen as early as 3 months in the patients treated with PROPECIA and led to a net increase in scalp hair count and hair regrowth. In addition, clinical studies demonstrated slowing of hair loss with PROPECIA by patient self-assessment. These effects were maintained through the second year of treatment. Maintenance of or improvement in clinical efficacy has also been demonstrated in controlled and open-extension studies for up to 3 years.

Ethnic Analysis of Clinical Data from Men

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs –19 hairs (PROPECIA vs placebo) among Caucasians (n=1,185), 49 vs –27 hairs among Blacks (n=84), 53 vs –38 hairs among Asians (n=17), 67 vs 5 hairs among Hispanics (n=45) and 67 vs -15 hairs among other ethnic groups (n=20). Patient self-assessment showed improvement across racial groups with PROPECIA treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall.

Study in Women

In a study involving 137 postmenopausal women with androgenetic alopecia who were treated with PROPECIA (n=67) or placebo (n=70) for 12 months, effectiveness could not be demonstrated. There was no improvement in hair counts, patient self-assessment, investigator assessment, or ratings of standardized photographs in the women treated with PROPECIA when compared with the placebo group (see INDICATIONS AND USAGE).

INDICATIONS AND USAGE

PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (See CLINICAL PHARMACOLOGY, *Clinical Studies*).

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated in women (see CLINICAL PHARMACOLOGY*, Clinical Studies* and CONTRAINDICATIONS).

PROPECIA is not indicated in children (see PRECAUTIONS, *Pediatric Use*).

CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy*.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

WARNINGS

PROPECIA is not indicated for use in pediatric patients (See INDICATIONS AND USAGE; and PRECAUTIONS, *Pediatric Use)* or women (See also PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*).

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*.)

PRECAUTIONS

General

Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Information for Patients

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, *Pregnancy;* and HOW SUPPLIED, *Storage and Handling.*) See also Patient Package Insert.

Drug/Laboratory Test Interactions

In clinical studies with PROPECIA in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking PROPECIA.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2,192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.05 μg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1,824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated) and in rats at a dose of $\geq$40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2,800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 μmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 μmol) used in *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1,824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,344 times the estimated human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the estimated human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease

in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS.

PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 μg/kg/day to 100 mg/kg/day (5-5,000 times the recommended human dose of 1 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥30 μg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (150 times the recommended human dose of 1 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (5000 times the recommended human dose of 1 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROPECIA is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Studies for PROPECIA (finasteride 1 mg) in the Treatment of Male Pattern Hair Loss

In controlled clinical trials for PROPECIA of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on PROPECIA and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROPECIA or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder (1.2%, 0.7%; primarily decreased volume of ejaculate:[0.8%, 0.4%]). Integrated analysis of clinical adverse experiences showed that during treatment with PROPECIA, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution occurred in all men who discontinued therapy with PROPECIA due to these side effects and in 58% of those who continued therapy.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (–8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that

finasteride at 5 times the dosage of PROPECIA (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

In the clinical studies with PROPECIA, the incidences for breast tenderness and enlargement, and for hypersensitivity reactions in finasteride-treated patients were not different from those in patients treated with placebo.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*

In controlled clinical trials for PROSCAR of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only one patient on PROSCAR (0.2%) and one patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROSCAR or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on PROSCAR for 24 to 48 months were similar to that observed in the 12-month controlled studies with PROSCAR. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

Adverse Effects Reported in Post-Marketing Experience for PROSCAR (finasteride 5 mg)

Breast tenderness and enlargement, as well as hypersensitivity reactions, including lip swelling and skin rash have been reported.

OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1,500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m^2 (400 mg/kg) and 5,900 mg/m^2 (1,000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg once a day.

PROPECIA may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

No. 6550 — PROPECIA tablets, 1 mg, are tan, octagonal, film-coated convex tablets with code MRK 71 on one side and PROPECIA 1 on the other. They are supplied as follows:

NDC 0006-0071-31 unit of use bottles of 30

NDC 0006-0071-61 ProPak™** - carton of 3 unit of use bottles of 30.

Storage and Handling

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy.*)

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued
Printed in USA

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PROPECIA™*
(Finasteride) Tablets
Patient Information about
PROPECIA® (Pro-pee-sha)
Generic name: finasteride
(fin-AS-tur-eyed)

PROPECIA is for use by MEN ONLY.**

Please read this leaflet before you start taking PROPECIA. Also, read the information included with PROPECIA each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss PROPECIA when you start taking your medication and at regular checkups.

What is PROPECIA used for?

PROPECIA is used for the treatment of male pattern hair loss on the vertex and the anterior mid-scalp area.

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PROPECIA is for use by **MEN ONLY** and should **NOT** be used by women or children.

What is male pattern hair loss?

Male pattern hair loss is a common condition in which men experience thinning of the hair on the scalp. Often, this results in a receding hairline and/or balding on the top of the head. These changes typically begin gradually in men in their 20s.

Doctors believe male pattern hair loss is due to heredity and is dependent on hormonal effects. Doctors refer to this type of hair loss as androgenetic alopecia.

Results of clinical studies:

For 12 months, doctors studied over 1800 men aged 18 to 41 with mild to moderate amounts of ongoing hair loss. All men, whether receiving PROPECIA or placebo (a pill containing no medication) were given a medicated shampoo (Neutrogena T/Gel® *** Shampoo). Of these men, approximately 1200 with hair loss at the top of the head were studied for an additional 12 months. In general, men who took PROPECIA maintained or increased the number of visible scalp hairs and noticed improvement in their hair in the first year, with the effect maintained in the second year. Hair counts in men who did not take PROPECIA continued to decrease.

In one study, patients were questioned on the growth of body hair. PROPECIA did not appear to affect hair in places other than the scalp.

Will PROPECIA work for me?

For most men, PROPECIA increases the number of scalp hairs, helping to fill in thin or balding areas of the scalp. Men taking PROPECIA noted a slowing of hair loss during two years of use. Although results will vary, generally you will not be able to grow back all of the hair you have lost. There is not sufficient evidence that PROPECIA works in the treatment of receding hairline in the temporal area on both sides of the head.

Male pattern hair loss occurs gradually over time. On average, healthy hair grows only about half an inch each month. Therefore, it will take time to see any effect.

You may need to take PROPECIA daily for three months or more before you see a benefit from taking PROPECIA. PROPECIA can only work over the long term if you continue taking it. If the drug has not worked for you in twelve months, further treatment is unlikely to be of benefit. If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment. You should discuss this with your doctor.

PROPECIA in not effective in the treatment of hair loss due to androgenetic alopecia in postmenopausal women. PROPECIA should not be taken by women.

How should I take PROPECIA?

Follow your doctor's instructions.

- Take one tablet by mouth each day.
- You may take PROPECIA with or without food.
- If you forget to take PROPECIA, do not take an extra tablet. Just take the next tablet as usual.

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PROPECIA will not work faster or better if you take it more than once a day.

Who should NOT take PROPECIA?

- PROPECIA is for the treatment of male pattern hair loss in **MEN ONLY** and should not be taken by women (see **A warning about PROPECIA and pregnancy**).
- PROPECIA should not be taken by children.
- Anyone allergic to any of the ingredients.

A warning about PROPECIA and pregnancy.

- **Women who are or may potentially be pregnant:**
  - **must not use PROPECIA**
  - **should not handle crushed or broken tablets of PROPECIA.**

If a woman who is pregnant with a male baby absorbs the active ingredient in PROPECIA, either by swallowing or through the skin, it may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a doctor should be consulted. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

What are the possible side effects of PROPECIA?

Like all prescription products, PROPECIA may cause side effects. In clinical studies, side effects from PROPECIA were uncommon and did not affect most men. A small number of men experienced certain sexual side effects. These men reported one or more of the following: less desire for sex; difficulty in achieving an erection; and, a decrease in the amount of semen. Each of these side effects occurred in less than 2% of men. These side effects went away in men who stopped taking PROPECIA. They also disappeared in most men who continued taking PROPECIA.

The active ingredient in PROPECIA is also used by older men at a five-times higher dose to treat enlargement of the prostate. Some of these men reported other side effects, including problems with ejaculation, breast swelling and/or tenderness and allergic reactions such as lip swelling and rash. In clinical studies with PROPECIA, these side effects occurred as often in men taking placebo as in those taking PROPECIA.

Tell your doctor promptly about these or any other unusual effects.

- **PROPECIA can affect a blood test called PSA (Prostate-Specific Antigen) for the screening of prostate cancer. If you have a PSA test done, you should tell your doctor that you are taking PROPECIA.**

Storage and handling.

Keep PROPECIA in the original container and keep the container closed. Store it in a dry place at room temperature. **PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.**

Do not give your PROPECIA tablets to anyone else. It has been prescribed only for you. Keep PROPECIA and all medications out of the reach of children.

THIS LEAFLET PROVIDES A SUMMARY OF INFORMATION ABOUT PROPECIA. IF AFTER READING THIS LEAFLET YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR.

1-800-830-7375, Monday through Friday, 8:30 A.M. TO 7:00 P.M. (ET).

MERCK & CO., INC.
Issued West Point, PA 19486, USA

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/s/

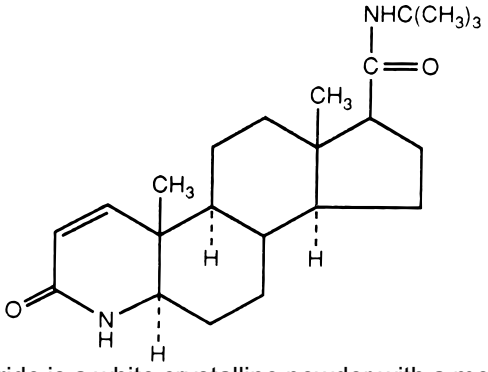
Jonathan Wilkin
12/8/01 04:41:20 PM

PROPECIA®
(Finasteride)
Tablets, 1 mg

DESCRIPTION

PROPECIA* (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250 C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

PROPECIA tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme (IC_{50}=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride

produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

A 48-week, placebo-controlled study designed to assess by phototrichogram the effect of PROPECIA on total and actively growing (anagen) scalp hairs in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total and anagen hair counts were obtained in a 1-cm^2 target area of the scalp. Men treated with PROPECIA showed increases from baseline in total and anagen hair counts of 7 hairs and 18 hairs, respectively, whereas men treated with placebo had decreases of 10 hairs and 9 hairs, respectively. These changes in hair counts resulted in a between-group difference of 17 hairs in total hair count ($p<0.001$) and 27 hairs in anagen hair count ($p<0.001$), and an improvement in the proportion of anagen hairs from 62% at baseline to 68% for men treated with PROPECIA. Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone, indicating that the hypothalamic-pituitary-testicular axis was not affected. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline in the first year of treatment, but these levels were within the physiologic range.

Pharmacokinetics

Following an oral dose of ^{14}C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possessed no more than 20% of the 5α-reductase inhibitory activity of finasteride.

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of AUC relative to a 5-mg intravenous dose infused over 60 minutes. Following intravenous infusion, mean plasma clearance was 165 mL/min (range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44-96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20-154 ng•hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng per day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys (see PRECAUTIONS, *Pregnancy*).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance, and a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 mL/min), the values for AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). Furthermore, finasteride has been well

tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Clinical Studies

Studies in Men

The efficacy of PROPECIA was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies, all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®** Shampoo) during the first 2 years of the studies.

There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. In addition, information was collected regarding sexual function (based on a self-administered questionnaire) and non-scalp body hair growth. The three studies were conducted in 1,879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1,553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

Studies in Men with Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial study and first extension periods (up to 2 years of treatment) and 60 men receiving placebo for the same periods. The extension studies were continued for 3 additional years, with 323 men on PROPECIA and 23 on placebo entering the fifth year of the study.

In order to evaluate the effect of discontinuation of therapy, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the first 12-month extension period. Some of these men continued in additional extension studies and were switched back to treatment with PROPECIA, with 32 men entering the fifth year of the study. Lastly, there were 543 men who received placebo for the initial 12 months followed by PROPECIA in the first 12-month extension period. Some of these men continued in additional extension studies receiving PROPECIA, with 290 men entering the fifth year of the study (see Figure below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, PROPECIA [n=679] vs placebo [n=672]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking PROPECIA for up to 2 years, resulting in a 138-hair difference between treatment groups ($p<0.001$, PROPECIA [n=433] vs placebo [n=47]) within the same area. In men treated with PROPECIA, the maximum improvement in hair count compared to baseline was achieved during the first 2 years. Although the initial improvement was followed by a slow decline, hair count was maintained above baseline throughout the 5 years of the studies. Furthermore, because the decline in the placebo group was more rapid, the difference between treatment groups also continued to increase throughout the studies, resulting in a 277-hair difference ($p<0.001$, PROPECIA [n=219] vs placebo [n=15]) at 5 years (see Figure below).

Patients who switched from placebo to PROPECIA (n=425) had a decrease in hair count at the end of the initial 12-month placebo period, followed by an increase in hair count after 1 year of treatment with PROPECIA. This increase in hair count was less (56 hairs above original baseline) than the increase (91 hairs above original baseline) observed after 1 year of treatment in men initially randomized to PROPECIA. Although the increase in hair count, relative to when therapy was initiated, was comparable between these two groups, a higher absolute hair count was achieved in patients who were started on treatment with PROPECIA in the initial study. This advantage was maintained through the remaining 3 years of the studies. A change of treatment from PROPECIA to placebo (n=48) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months (see Figure below).

At 12 months, 58% of men in the placebo group had further hair loss (defined as any decrease in hair count from baseline), compared with 14% of men treated with PROPECIA. In men treated for up to 2 years, 72% of men in the

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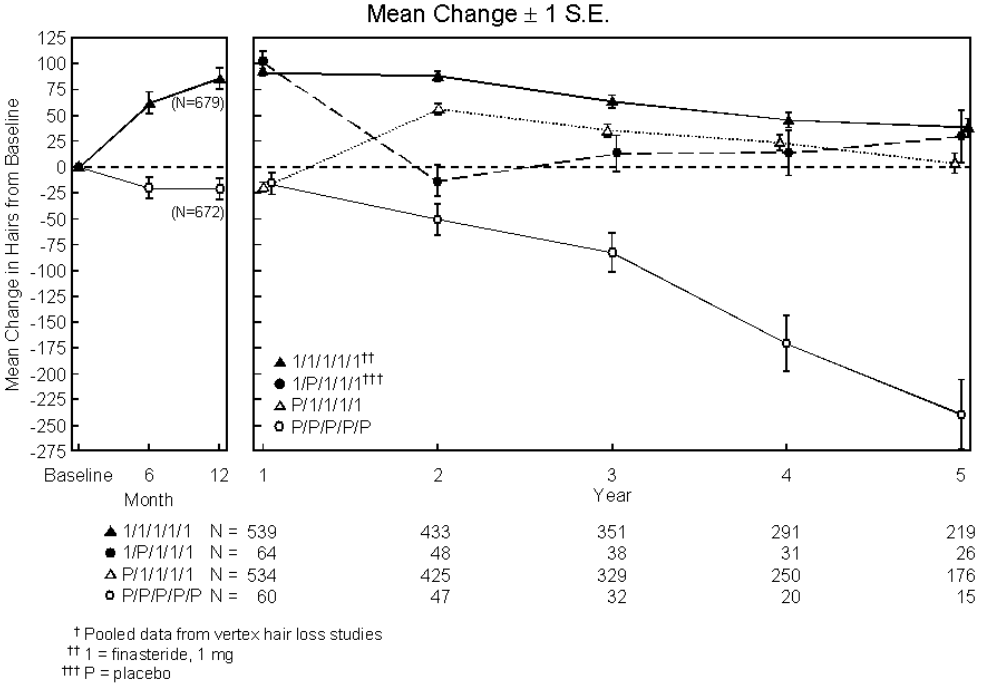
placebo group demonstrated hair loss, compared with 17% of men treated with PROPECIA. At 5 years, 100% of men in the placebo group demonstrated hair loss, compared with 35% of men treated with PROPECIA.

Effect on Hair Count†
Number of Hairs in a 1-Inch Diameter Circle
Mean Change ± 1 S.E.



	Baseline	Month 6	Month 12	Year 1	Year 2	Year 3	Year 4	Year 5
▲ 1/1/1/1/1	N = 539			433		351	291	219
● 1/P/1/1/1	N = 64			48		38	31	26
△ P/1/1/1/1	N = 534			425		329	250	176
○ P/P/P/P/P	N = 60			47		32	20	15

† Pooled data from vertex hair loss studies
†† 1 = finasteride, 1 mg
††† P = placebo

Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with PROPECIA. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with improvement maintained over 5 years.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with PROPECIA compared with placebo as early as 3 months ($p<0.001$). At 12 months, the investigators rated 65% of men treated with PROPECIA as having increased hair growth compared with 37% in the placebo group. At 2 years, the investigators rated 80% of men treated with PROPECIA as having increased hair growth compared with 47% of men treated with placebo. At 5 years, the investigators rated 77% of men treated with PROPECIA as having increased hair growth, compared with 15% of men treated with placebo.

An independent panel rated standardized photographs of the head in a blinded fashion based on increases or decreases in scalp hair using the same 7-point scale as the investigator assessment. At 12 months, 48% of men treated with PROPECIA had an increase as compared with 7% of men treated with placebo. At 2 years, an increase in hair growth was demonstrated in 66% of men treated with PROPECIA, compared with 7% of men treated with placebo. At 5 years, 48% of men treated with PROPECIA demonstrated an increase in hair growth, 42% were rated as having no change (no further visible progression of hair loss from baseline) and 10% were rated as having lost hair when compared to baseline. In comparison, 6% of men treated with placebo demonstrated an increase in hair growth, 19% were rated as having no change and 75% were rated as having lost hair when compared to baseline.

Other Results in Vertex Baldness Studies

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo

were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. PROPECIA did not appear to affect non-scalp body hair.

Study in Men with Hair Loss in the Anterior Mid-Scalp Area

A study of 12-month duration, designed to assess the efficacy of PROPECIA in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Summary of Clinical Studies in Men

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with PROPECIA or placebo received a tar-based shampoo (Neutrogena T/Gel®** Shampoo) during the first 2 years of the studies. Clinical improvement was seen as early as 3 months in the patients treated with PROPECIA and led to a net increase in scalp hair count and hair regrowth. In clinical studies for up to 5 years, treatment with PROPECIA slowed the further progression of hair loss observed in the placebo group. In general, the difference between treatment groups continued to increase throughout the 5 years of the studies.

Ethnic Analysis of Clinical Data from Men

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs -19 hairs (PROPECIA vs placebo) among Caucasians (n=1,185), 49 vs -27 hairs among Blacks (n=84), 53 vs -38 hairs among Asians (n=17), 67 vs 5 hairs among Hispanics (n=45) and 67 vs -15 hairs among other ethnic groups (n=20). Patient self-assessment showed improvement across racial groups with PROPECIA treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall.

Study in Women

In a study involving 137 postmenopausal women with androgenetic alopecia who were treated with PROPECIA (n=67) or placebo (n=70) for 12 months, effectiveness could not be demonstrated. There was no improvement in hair counts, patient self-assessment, investigator assessment, or ratings of standardized photographs in the women treated with PROPECIA when compared with the placebo group (see INDICATIONS AND USAGE).

INDICATIONS AND USAGE

PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (See CLINICAL PHARMACOLOGY, *Clinical Studies*).

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated in women (see CLINICAL PHARMACOLOGY, *Clinical Studies* and CONTRAINDICATIONS).

PROPECIA is not indicated in children (see PRECAUTIONS, *Pediatric Use*).

CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy*.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

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WARNINGS

PROPECIA is not indicated for use in pediatric patients (See INDICATIONS AND USAGE; and PRECAUTIONS, *Pediatric Use*) or women (see also PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*).

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (see also CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*.)

PRECAUTIONS

General

Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Information for Patients

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*.) See also Patient Package Insert.

Drug/Laboratory Test Interactions

In clinical studies with PROPECIA in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking PROPECIA.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2,192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.05 μg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1,824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated) and in rats at a dose of $\geq$40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2,800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 μmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 μmol) used in *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1,824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,344 times the estimated human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the estimated human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS.

PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 μg/kg/day to 100 mg/kg/day (5-5,000 times the recommended human dose of 1 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥30 μg/kg/day (≥1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (150 times the recommended human dose of 1 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (5000 times the recommended human dose of 1 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROPECIA is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical efficacy studies with PROPECIA did not include subjects aged 65 and over. Based on the pharmacokinetics of finasteride 5 mg, no dosage adjustment is necessary in the elderly for PROPECIA (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). However the efficacy of PROPECIA in the elderly has not been established.

ADVERSE REACTIONS

Clinical Studies for PROPECIA (finasteride 1 mg) in the Treatment of Male Pattern Hair Loss

In controlled clinical trials for PROPECIA of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on PROPECIA and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROPECIA or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder (1.2%, 0.7%; primarily decreased volume of ejaculate: [0.8%, 0.4%]). Integrated analysis of clinical adverse experiences showed that during treatment with PROPECIA, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution occurred in men who discontinued therapy with PROPECIA due to these side effects and in most of those who continued therapy. The incidence of each of the above side effects decreased to ≤ 0.3% by the fifth year of treatment with PROPECIA.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of PROPECIA (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

In the clinical studies with PROPECIA, the incidences for breast tenderness and enlargement, hypersensitivity reactions, and testicular pain in finasteride-treated patients were not different from those in patients treated with placebo.

Postmarketing Experience for PROPECIA (finasteride 1 mg)

Breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*

In controlled clinical trials for PROSCAR of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only one patient on PROSCAR (0.2%) and one patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROSCAR or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on PROSCAR for 24 to 48 months were similar to that observed in the 12-month controlled studies with PROSCAR. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1,500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m^2 (400 mg/kg) and 5,900 mg/m^2 (1,000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg once a day.

PROPECIA may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit, which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

No. 6642— PROPECIA tablets, 1 mg, are tan, octagonal, film-coated convex tablets with “stylized P” logo on one side and PROPECIA on the other. They are supplied as follows:

NDC 0006-0071-31 unit of use bottles of 30

NDC 0006-0071-61 PROPAK®*** - carton of 3 unit of use bottles of 30.

Storage and Handling

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy*.)

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued MONTH YEAR
Printed in USA

*** Registered trademark of MERCK & CO., INC.

PROPECIA®* [Logo]
(Finasteride) Tablets
Patient Information about
PROPECIA® (Pro-pee-sha)
Generic name: finasteride
(fin-AS-tur-eyed)

PROPECIA is for use by MEN ONLY.**

Please read this leaflet before you start taking PROPECIA. Also, read the information included with PROPECIA each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss PROPECIA when you start taking your medication and at regular checkups.

What is PROPECIA used for?

PROPECIA is used for the treatment of male pattern hair loss on the vertex and the anterior mid-scalp area.

PROPECIA is for use by **MEN ONLY** and should **NOT** be used by women or children.

What is male pattern hair loss?

Male pattern hair loss is a common condition in which men experience thinning of the hair on the scalp. Often, this results in a receding hairline and/or balding on the top of the head. These changes typically begin gradually in men in their 20s.

Doctors believe male pattern hair loss is due to heredity and is dependent on hormonal effects. Doctors refer to this type of hair loss as androgenetic alopecia.

Results of clinical studies:

For 12 months, doctors studied over 1800 men aged 18 to 41 with mild to moderate amounts of ongoing hair loss. Of these men, approximately 1200 with hair loss at the top of the head participated in additional extension studies, resulting in a total study time of up to five years. In general, men who took PROPECIA maintained or increased the number of visible scalp hairs and noticed improvement in their hair in the first year. Improvement, compared to the start of the study, was maintained through the remaining years of treatment. Hair counts in men who did not take PROPECIA continued to decrease.

In one study, patients were questioned on the growth of body hair. PROPECIA did not appear to affect hair in places other than the scalp.

Will PROPECIA work for me?

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* Registered trademark of MERCK & CO., Inc.
** Registered trademark of MERCK & CO., Inc.

For most men, PROPECIA increases the number of scalp hairs in the first year of treatment, helping to fill in thin or balding areas of the scalp. In addition, men taking PROPECIA may note a slowing of hair loss. Although results will vary, generally you will not be able to grow back all of the hair you have lost. There is not sufficient evidence that PROPECIA works in the treatment of receding hairline in the temporal area on both sides of the head.

Male pattern hair loss occurs gradually over time. On average, healthy hair grows only about half an inch each month. Therefore, it will take time to see any effect.

You may need to take PROPECIA daily for three months or more before you see a benefit from taking PROPECIA. PROPECIA can only work over the long term if you continue taking it. If the drug has not worked for you in twelve months, further treatment is unlikely to be of benefit. If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment. You should discuss this with your doctor.

PROPECIA is not effective in the treatment of hair loss due to androgenetic alopecia in postmenopausal women. PROPECIA should not be taken by women.

How should I take PROPECIA?

Follow your doctor's instructions.

- Take one tablet by mouth each day.
- You may take PROPECIA with or without food.
- If you forget to take PROPECIA, do not take an extra tablet. Just take the next tablet as usual.

PROPECIA will not work faster or better if you take it more than once a day.

Who should NOT take PROPECIA?

- PROPECIA is for the treatment of male pattern hair loss in **MEN ONLY** and should not be taken by women (see **A warning about PROPECIA and pregnancy**).
- PROPECIA should not be taken by children.
- Anyone allergic to any of the ingredients.

A warning about PROPECIA and pregnancy.

- **Women who are or may potentially be pregnant:**
  - **must not use PROPECIA**
  - **should not handle crushed or broken tablets of PROPECIA.**

If a woman who is pregnant with a male baby absorbs the active ingredient in PROPECIA, either by swallowing or through the skin, it may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a doctor should be consulted.

PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

What are the possible side effects of PROPECIA?

Like all prescription products, PROPECIA may cause side effects. In clinical studies, side effects from PROPECIA were uncommon and did not affect most men. A small number of men experienced certain sexual side effects. These men reported one or more of the following: less desire for sex; difficulty in achieving an erection; and, a decrease in the amount of semen. Each of these side effects occurred in less than 2% of men. These side effects went away in men who stopped taking PROPECIA. They also disappeared in most men who continued taking PROPECIA.

In general use, the following have been reported: allergic reactions including rash, itching, hives and swelling of the lips and face; problems with ejaculation; breast tenderness and enlargement; and testicular pain.

Tell your doctor promptly about these or any other unusual side effects.

- **PROPECIA can affect a blood test called PSA (Prostate-Specific Antigen) for the screening of prostate cancer. If you have a PSA test done, you should tell your doctor that you are taking PROPECIA.**

Storage and handling.

Keep PROPECIA in the original container and keep the container closed. Store it in a dry place at room temperature. **PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.**

Do not give your PROPECIA tablets to anyone else. It has been prescribed only for you. Keep PROPECIA and all medications out of the reach of children.

THIS LEAFLET PROVIDES A SUMMARY OF INFORMATION ABOUT PROPECIA. IF AFTER READING THIS LEAFLET YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR.

1-888-637-2522, Monday through Friday, 8:30 A.M. TO 7:00 P.M. (ET).

www.propecia.com

Issued Month Year

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
4/10/02 06:24:43 PM

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

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IN RE: PROPECIA (FINASTERIDE) PRODUCTS LIABILITY LITIGATION	:	Master File No. 1:12-md-02331-BMC-PK
	:	MDL No. 2331
This Document Relates to:	:	Honorable Brian M. Cogan
ALL CASES	:	Magistrate Judge Judge Peggy Kuo

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May 19, 2016

Confidential - Subject to Protective Order

Oral sworn videotape deposition of CHARLOTTE B. MERRITT, taken at the Short Hills Hilton, John F. Kennedy Parkway, Short Hills, New Jersey, 08078, before Patricia R. Frank, Certified Court Reporter and Notary Public of the State of New Jersey, commencing at 9:31 a.m., on the above date.

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let's look to the next label.

(Letter from Dr. Wilkin to Dr. Rozycki and attached 2002 Propecia label marked Exhibit No. 210 for identification.)

BY MR. FISHER:

Q. This is a label from 2002, Exhibit 210. When you're ready, if you turn to the adverse event section -- adverse reaction section in this exhibit, please? It's on page 11.

A. Okay.

Q. You're there on page 11, adverse reactions?

A. Yes.

Q. And you see that here it's still just limited to the 12-month data, right?

MR. HUDSON: Objection.

Q. It begins, "In controlled clinical trials for Propecia of 12-month duration" -- and goes on, right?

MR. HUDSON: Objection.

THE WITNESS: It mentions the fifth year of treatment at the end of that paragraph.

Q. I'm going to come to that. That's right. I'm going to come to that in a moment.

At the beginning it says, "In controlled

clinical trials for Propecia of 12 months" -- and it reports the findings, right?

A. It reports the 12-month incidences, yes.

Q. And if you drop down to the second to last paragraph -- second to last sentence in that paragraph, it states, "Resolution occurred in men who discontinued therapy."

Do you see that?

A. Yes.

Q. So the word "all" has been removed in this label.

A. Yes, it has.

Q. Why was that?

A. Well, as you saw, there were some men in whom after some period of time the AEs did not resolve so this is -- so the word "all" was no longer factual as relates to the longer term data beyond the initial period of the trial.

Q. The sentence has also been changed to take out "58 percent" and replace it with the word "most." Do you see that?

A. Yes.

Q. And you would agree with me that the only change that reflects the fact that there were in fact men who had -- who did not have resolution upon

discontinuation, the only thing that reflects that here is the taking out of the word "all," right?

MR. HUDSON: Objection. Go ahead.

Q. It doesn't also say there were men who did not experience resolution upon discontinuation, right?

A. No, it doesn't say that.

MR. HUDSON: Objection.

Q. And then as you point out, in the last sentence that's been -- the new sentence there, it says, "The incidence of each of the above side effects decreased to less than or equal to 0.3 percent by the fifth year of treatment with Propecia," right?

A. Yes.

Q. Okay. So that's a reference to the fifth year, but there's no reference anywhere else to years two, three or four, right?

A. No, there's not.

Q. Well, isn't this precisely what Dr. Kaufman said in his 2000 e-mail was deceptive, to simply report on the results in the fifth year of the study and not --

A. It's not --

MR. HUDSON: Objection.

THE WITNESS: It's not simply reporting on the fifth year. It's got a big, long paragraph with a whole lot more data on the first year which is the most relevant year.

BY MR. FISHER:

Q. The last sentence which has been added refers only to the fifth year and to the incidence of the adverse events in the fifth year data, right?

A. Yes, following the description of the one year data.

Q. And there's nothing about the two, three or four year data. We've established that, right?

A. Not in this paragraph, no.

Q. So you don't think that just reporting on the incidence in the fifth year alone is deceptive to use Dr. Kaufman's term?

MR. HUDSON: Objection.

THE WITNESS: It's not reporting on the fifth year alone. It's reporting on the first year, which was the largest year of the study and the most placebo controlled because the patients were balanced between treatment groups and the end of the study.

BY MR. FISHER:

Q. That one sentence states that the

incidence of each of the above side effects decreased to less than or equal to 0.3 percent by the fifth year, right?

A. That is what it says.

Q. And wasn't Dr. Kaufman explaining that the reason that that occurred was because the men with sexual side effects had in many instances dropped out of the study?

MR. HUDSON: Objection.

Q. Isn't that why you can report on a number like 0.3 percent here?

MR. HUDSON: Objection.

THE WITNESS: Side effects occur usually earlier on in treatment, so men that have been treated for five years are unlikely to report a lot of side effects. Keith was objecting to this number being presented -- in the flip side of this number being presented in isolation without the entire perspective of a higher incidence of AEs that was reported earlier on in the study, which is what's presented in the label quite clearly.

BY MR. FISHER:

Q. Okay. But this does not go on to say that the reason or a reason that there is only 0.3 percent experiencing these side effects in the fifth

year is because most of them have already dropped out of the study; it doesn't say that, does it?

MR. HUDSON: Objection.

THE WITNESS: It does not say that.

Q. You see that there has also been added a post-marketing experience for Propecia in this 2002 label, right?

A. Yes.

Q. And it reports on breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria and swelling of the lips and face and testicular pain. Right?

A. Yes.

Q. There's no reference in this post-marketing experience section to sexual dysfunction, adverse events such as those listed above from the clinical trials.

A. No. The guidance for post-marketing sections and labeling in general is not to repeat side effects that you already have reported as part of clinical studies but to present additional side effects that are -- that are new, that didn't show up in clinical trials.

Q. All right. And so that's why those sexual dysfunction adverse events are not reported

in the post-marketing experience section?

A. Yes, because they're already labeled.

Q. Just -- I think we established this, but in changing this label in 2002 from the one we looked at in 2001, there was nothing that prevented Merck from disclosing the details that were set forth in the Patrick Ruane memo about patients continuing to experience sexual adverse events upon discontinuation, right?

MR. HUDSON: Object to form.

THE WITNESS: When Merck submitted the five year data to FDA, which it would have had to do in order to get this statement and any other statement that's in here relating to those extension studies, it would have gone with a clinical study report that included all data on all AEs, including the outcome of the AE, whether it resolved or not, so whatever version of this, and we established that this Exhibit Number, what does that say, 32 --

Q. Fifty-two.

A. -- 52 was at that particular point in time. Whatever version of the data were the truth at the time we submitted the labeling supplement to FDA would have been accompanied by those data.

Q. Well, that's not what I asked you. What

I asked you is there was nothing that prevented Merck, which as we agreed earlier is responsible at all times for its label, from putting into this 2002 label what it now had information about for over a year, namely from November -- at least as early as November of 2000, about the lack of resolution upon discontinuation in some patients in the clinical data, right?

A. I apologize.

MR. HUDSON: Objection.

THE WITNESS: I thought your question was -- you know, I interpreted your question to mean there was nothing that prevented Merck from sharing those data with FDA which certainly we did.

Merck didn't feel at the time that that was something that needed to be -- that needed to be put in the label. FDA apparently agreed. This is the label that was -- you know, that was the results of that submission, and we can't comment any further.

BY MR. FISHER:

Q. Well, just to be clear from what we've talked about before the first break, it's not FDA's responsibility for this label; it's Merck's responsibility to update its label and keep it

current and accurate, right?

A. It is Merck's responsibility; but when Merck submits data to FDA, it's their responsibility to review it and to oversee that process and to agree with it or not, and in this case they agreed with it.

Q. I don't think you're testifying that you actually proposed in this 2002 label to divulge more information about the clinical trial data as set forth in Mr. Ruane's memo and that FDA declined to put it in; you're not saying that, are you?

A. No, I'm not.

Q. With respect to the label language itself, Merck could have developed this language and made it more clear that there were instances of patients developing sexual adverse events in the clinical data, in the clinical trials, whose sexual adverse events did not resolve upon discontinuation, right?

MR. HUDSON: Objection.

THE WITNESS: It could have been done if Merck felt that that was an appropriate thing to label based on the data. I can't comment on why -- why it was done the way it was done. It's been too long, and I can't recall the details of the data;

but a lot of things, you know, go into those types of decisions in terms of the quality of the -- of the report and the particular circumstances.

MR. FISHER: All right. Did you want to take a break?

MR. HUDSON: Yeah, let's --

THE VIDEOGRAPHER: We're going off the record. The time is 12:06 p.m.

(Brief recess.)

THE VIDEOGRAPHER: We're back on the record at 1:13 p.m.

BY MR. FISHER:

Q. Good afternoon.

A. Good afternoon.

Q. We spoke earlier this morning about the application process in Europe. Do you recall that?

A. Yes.

Q. And we noted that the -- in the case of Propecia, that the Swedish agency was the Reference Member Nation --

A. Yes.

Q. -- State for the EU, and that meant that they were responsible for -- in the case of Propecia in the EU countries, it was the Swedish agency that made determinations about safety and efficacy and

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

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IN RE: PROPECIA (FINASTERIDE) PRODUCTS LIABILITY LITIGATION	:	Master File No. 1:12-md-02331-BMC-PK
	:	MDL No. 2331
This Document Relates to: ALL CASES	:	Honorable Brian M. Cogan
	:	Magistrate Judge Peggy Kuo

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April 19, 2016

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Confidential videotape deposition of CYNTHIA GROSSEL SILBER, M.D., taken pursuant to notice, was held at the law offices of Morgan, Lewis & Bockius LLP, 1701 Market Street, 18th Floor, Philadelphia, Pennsylvania, beginning at 8:14 a.m., on the above date, before Kimberly A. Cahill, a Federally Approved Registered Merit Reporter and Notary Public.

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bullet point 1 here on your resume of signal detection and safety surveillance -- do you see that?

A. Uh-hum.

Q. -- what did you specifically do to determine whether or not there was a safety signal related to an association between Propecia and persistent sexual dysfunction following discontinuation of use?

A. Whether there was a signal?

Q. Yes.

A. Is that the question?

Q. No. The question is, what did you do to determine whether or not a signal existed?

A. When I picked up the product, the issue was already one that was under ongoing analysis in the program, so I did not do signal detection for this particular adverse event.

Q. So let me make sure I totally have that clear. So from whatever the date was, whether it was

2006 or '7 or '8 or whenever you joined the Propecia team, is it your testimony you never engaged in signal detection related to Propecia and persistent ongoing sexual dysfunction?

A. I engaged in signal evaluation. The signal had been identified by the time I joined the program. It had already been reviewed.

Q. So let me go back and get a sense what that means. Are you saying that there was a signal that was identified between Propecia and persistent sexual dysfunction prior to your joining the team?

A. Prior to my joining the team, there was investigation of that product-event combination, yes.

Q. And what was the outcome?

A. The outcome when I joined the team was that persistent erectile dysfunction was not causally associated with Propecia.

Q. So there was no signal by

the time you -- when you joined the team, the view of Merck was that there was no signal establishing an association between Propecia and persistent ongoing sexual dysfunction following discontinuation of use?

A. I don't think I would say there was -- there had been a signal and we were following it on an ongoing basis.

Q. Okay. So that --

A. It's a product-event combination. That's all it is.

Q. I get that. A signal, just so -- let's make it clear for the jury --

A. Uh-hum.

Q. -- a signal does not equate to causation. Right?

A. Correct.

Q. But a signal is, like, if you were to -- if you're building a puzzle, okay, you got lots of pieces in the puzzle. Right?

A. Uh-hum.

Q. Yes?

A. Yes.
Q. You got the border and then you got the inner parts. Right?
A. Yes.
Q. And the puzzle has a picture. Right?
A. Yes.
Q. And you're trying to figure out what that picture is by putting those pieces together. Right?
A. Yes.
Q. And a signal is a piece of the puzzle that might lead to a conclusion that a particular outcome is causative; correct?
MR. HARRELL: Object to form.
THE WITNESS: I'm sorry. I don't follow your analogy.
BY MR. BECKER:
Q. A signal might establish an association between a drug and a negative outcome; correct?
MR. HARRELL: Object to

form.

THE WITNESS: A signal is the beginning of the process of evaluation.

BY MR. BECKER:

Q. Right. It's one piece in the puzzle. Right? As you try and build this picture to get to whether or not the drug causes a particular outcome. True?

MR. HARRELL: Object to form.

Go ahead.

THE WITNESS: I'm sorry. I'm just not -- I'm not following the analogy.

BY MR. BECKER:

Q. Okay. Well, let me make sure I understand what you're saying clearly. Had Merck identified a signal -- I'm not asking if they agreed that it was causative or not, but prior to your arrival, when you joined the Propecia team, had Merck identified a signal existed between Propecia and ongoing

sexual dysfunction following discontinuation of use?

A. Yes.

Q. And you joined the team sometime in the 2007-2008 timeframe to the best of your recollection?

MR. HARRELL: Object to form; asked and answered.

BY MR. BECKER:

Q. Let me put it this way: You joined the team well before 2012; correct?

A. Yes.

Q. And Merck did not amend its label in the United States to tell men about the association, this signal you had identified, between Propecia and persistent ongoing sexual dysfunction following discontinuation of use until April of 2012; correct?

A. I --

MR. HARRELL: Object to form.

THE WITNESS: -- object to

the -- I object to the word association.

BY MR. BECKER:

Q. Okay. Well, you don't get the right to object. You get to answer my questions and your lawyer gets to object --

A. Well --

Q. -- so I'll ask you again: You testified earlier that somebody had established a signal between Propecia and persistent ongoing sexual dysfunction prior to you joining the team in the mid 2000s; correct?

A. Yes.

Q. And it would take another four, five, six years till that signal was indicated in the warning label here in the United States; correct?

MR. HARRELL: Object to form.

Go ahead.

THE WITNESS: I was not objecting in a legal sense to the

use of the word association.

So I would say a couple of things. I would say --

MR. BECKER: Stop. I'm -- no, no, no --

MR. HARRELL: She gets to answer her question.

MR. BECKER: No, she gets to answer the question that I asked.

MR. HARRELL: You can't cut her off while she's answering.

MR. BECKER: But then she gets to answer -- I don't have a judge here so I can't stop her as nonresponsive.

MR. HARRELL: I'm sorry, but you asked a question and she's answering.

MR. BECKER: I asked a yes/no question.

MR. HARRELL: You let her answer the question.

MR. BECKER: I'm going to withdraw the question.

BY MR. BECKER:

Q. When was the first time that the United States warning label discussed a potential signal between -- a potential association between persistent ongoing sexual dysfunction following discontinuation of use and Propecia?

A. I believe it was between the end of 2010 and the beginning of 2011.

Q. There was a warning label -- you have an understanding that Merck put in a CBE regarding erectile dysfunction in 2011; correct?

A. Yes.

Q. And you have an understanding that the FDA amended the language from Merck's CBE and expanded it to sexual dysfunction in 2012. True?

A. Yes.

Q. And that was the first time that this potential association was discussed in the United States warning label; correct?

A. Yes.

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF NEW YORK

IN RE: PROPECIA (FINASTERIDE) PRODUCTS LIABILITY LITIGATION	Master File No. 1:12-md-02331-BMC-PK MDL NO. 2331
This Document Relates to: ALL CASES	Honorable Brian M. Cogan Magistrate Judge Peggy Kuo

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Videotaped Deposition of PAUL HOWES, taken before and by Janis L. Ferguson, RPR, CRR, Notary Public and for the Commonwealth of Pennsylvania, on Tuesday, June 7, 2016, commencing at 9:34 a.m., at the Penn Stater Hotel and Conference Center, 215 Innovation Boulevard, State College, PA 16803.

Reported by Janis L. Ferguson

Registered Professional Reporter

Certified Realtime Reporter

the video record.

MR. BECKER: All right. So off the record we had a brief colloquy with counsel. We don't have an ELMO, and our computer is not hooked up to the screen. So in lieu of putting -- we might put one picture up a little bit later. But in lieu of putting up documents on the screen, we have an agreement that if and when we go to trial, and if the document is offered and accepted into evidence or offered for use at trial, we can refer to the document that we discussed during the deposition, or those portions of it in the picture and picture context with the witnesses. Is that basically our agreement?

MR. MORROW: Agreed.

MR. BECKER: Okay.

BY MR. BECKER:

Q. All right. Now, Mr. Howes, I'm showing you an article from the Wall Street Journal dated August 12th, 1997 entitled "Bet on Fewer Blockbusters". Do you see that there?

A. Yes.

Q. Okay. Direct -- let me direct your attention

to the first paragraph of the document. It says, "Some of the nation's best-known prescription drugs are on the brink of a sales plunge, and drugmakers are scrambling to survive it. About 40 drugs with 16 billion in sales last year -- one-quarter of the industry's U.S. revenues and an even higher percentage of total profits for some companies -- are set to lose patent protection by the end of 2002."

Did I read that correctly?

A. Yes.

Q. Okay. During this period of time -- and by "this period", I mean the late '90s to early 2007 -- Merck was facing the loss of several key patents with respect to significant drugs that produced large volumes of revenue for the company. Correct?

MR. MORROW: Objection. You may answer.

A. Yeah. Patent expires are known years in advance of when they occur.

Q. Right. And there were a series of drugs that were going to go off patent in this 1997 to 2002 time frame that Merck possessed the patent to, right?

A. Yes.

Q. Okay. Now, as a relatively high-ranking member at Merck, you had an understanding that

patent protection affords the company a monopoly on its ability to sell certain drugs. Correct?

MR. MORROW: Objection.

A. Yes.

Q. And as a result of that monopoly, you have the ability to engage in premium pricing or brand pricing for a particular pharmaceutical. Correct?

MR. MORROW: Objection. You may answer.

A. Pricing -- in this period of time, pricing on an annual basis went up generally less than the rate of inflation. It was very predictable.

Q. What I'm getting at is that you can't sell it --

A. Right. Illegal competition is not permitted until the patent expires.

Q. Okay. A couple of things -- and I didn't go over the rules of deposition before, and I apologize. So depositions are a very weird way of communicating. You knew exactly where I was going with that question, and you answered it. But because of the fact that -- if we were having a real conversation, we would do that. But in a deposition, I have to ask my question, and then you have to answer. Otherwise, it reads really poorly on --

A. Okay.
Q. -- on the deposition.
And the other thing, too, your lawyer from time to time is going to object. Unless he tells you not to answer the question, allow him to put his objection on the record, and then go ahead and answer it. Okay?
A. So if he states an objection, I should wait until he finishes --
Q. When he's done with his objection, then you may go ahead and answer, unless he tells you not to. Okay.
A. Thank you.
Q. All right. So patent protection, generally speaking -- I'm not asking for a legal conclusion -- affords the company to be the sole distributor of that product in the marketplace. Correct?
A. Yes.
Q. Okay. So, for example, you had during this time period a statin that you were selling. Right?
A. Yes.
Q. Okay. And you, as the -- you were the only company, as a result of your patent protection, that could sell that statin. Right?

A. Correct.
Q. Now, when that patent expired, that allowed competitors to come into the marketplace. Right?
A. Yes.
Q. And you could no longer sell that patent for the price -- or sorry. You could no longer sell that product for the price you were selling it at. True?
MR. MORROW: Objection.
A. (No response.)
Q. I mean, you could sell it, but nobody would buy it. Right?
A. People did buy it. Fewer people bought it.
Q. Right. When a patent expires, is it fair to say that the generics tend to take over the market?
A. Over time, they do, yes.
Q. And that's because the generics --
A. For that single chemical entity. There are other statins.
Q. Right. I'm only talking about --
A. Right.
Q. -- that one product.
A. Yeah.
Q. And the reason that the generics tend to take over the market over time is because for that same

chemical entity, they are charging less than what the brand manufacturer, like Merck, is charging. True?

A. Yes.

Q. Okay. So during this time period, from 1997 through 2002, you were aware of the fact that Merck faced a large number of expiring patents related to key drugs it was selling. Right?

MR. MORROW: Objection.

A. Correct.

Q. Okay. In fact, if you look at Exhibit 227, directing your attention to about a third of the way down the page where it says "at the epicenter"? Do you see that?

A. Yes.

Q. "At the epicenter of the patent expiration quake is giant Merck and Company, which will lose a lock on four drugs that provide more than half of its 6.18 billion U.S. drug sales last year, including heart drugs Vasotec and Mevacor."

Do you see that?

A. Yes.

Q. Okay. So during this time period, prior to the launch of Propecia, Merck was aware of the fact that at least half of its revenue related to four key

drugs --

A. U.S. revenue.

Q. U.S. revenue -- was going to face competition from generic entrants into the marketplace. Right?

A. Correct.

Q. And that's not necessarily a good thing for the company, is it?

MR. MORROW: Objection.

A. It all depends on what else is going on with the company, I would say. So it's -- of course, if it doesn't happen, that is better. The fact that it does happen is known. It's predictable. Maybe you're going to show me what their revenues worldwide were each of the following years, what the profitability was. But it's -- it's all --

Q. Something you have to plan for, right?

A. You have to plan for, correct.

Q. And there's a couple of different ways that you can plan to confront generic entrants into the market. Correct?

A. Yes.

Q. Okay. One of those ways is that you can develop your own generic pharmaceuticals. Correct?

A. Yes.

(Deposition Exhibit 228 - New York Times article titled "Merck Sets Generic Drug Sales" - marked for identification.)

Q. Okay. Let me show you what I've marked as Exhibit 228. Keep 227 there. We're going to come back to it.

This is an article from the New York Times dated September 8th, 1992 entitled "Merck Sets Generic Drug Sales".

(Discussion held off the record.)

Q. It's a long table. I've give you two, and you can just pass one to Chip.

All right. So recognizing that it was going to face a number of key drugs going off patent, Merck developed some strategies to -- to backfill in the revenue it anticipated to lose from those particular products. Correct?

A. Yes.

Q. And one of the methods it chose to undertake was to develop or enter into the generic market. Correct?

A. Yes.

Q. Okay. Specifically, the very first paragraph of this article says, quote, "An announcement by Merck

& Company that it would market lower-priced generic versions of its products signals that even the world's most powerful drug companies cannot ignore the possibility of sharp revenue decline when important drugs lose patent protection."

Did I read that correctly?

A. Yes.

Q. Okay. So one of the things that you did to fend off that loss of revenue was to start to compete in the generic marketplace.

MR. MORROW: Objection.

Q. True?

MR. MORROW: Objection.

A. Yes.

Q. Turn to the next page of the packet.

A. (Witness complies.)

Q. The last paragraph of this article says, "Merck also has a joint venture with Johnson & Johnson to sell over-the-counter versions of Merck drugs, notably Pepcid, an ulcer treatment whose patent expires in August 2000. Analysts said Merck might end up selling Pepcid in three forms; the original, a generic, and a non-prescription version."

Did I read that correctly?

A. Yes.
Q. Okay. So a second way that you can compete with expiring patents is that you can take a drug and make it -- or ask the FDA to make it non-prescription. Correct?
A. Yes.
Q. That means over-the-counter. Right?
A. Correct.
Q. And, in fact, that's what you did with Pepcid. Right?
A. With a different strength of the Pepcid.
Q. Right. So today -- I mean, if the jury goes out and is looking for acid reflux medicine, they can buy Pepcid AC over the counter. Right?
A. Yes.
Q. Okay. And that's a revenue source for Merck. Right?
A. Yes.
Q. But it's fair to say that of the three types of revenue sources you have, brand, generic, and over the counter, the way you make the most money, the most revenue, is through the sale of brand drugs. Correct?
A. Correct.
MR. MORROW: Objection.

Q. And so the third way that you decided -- that the company tried to fend off this loss of patent protection was to, in fact, develop new drugs. True?
A. Yes.
Q. Go back to Exhibit 227, if you would.
A. (Witness complies.)
Q. Directing your attention to the first page of the document, about two-thirds of the way down, do you see the sentence that starts with "to avert calamity"?
A. Um-hum.
Q. It says, "To avert calamity, major pharmaceutical companies are racing to find new drugs to replace the billions in dollars in sales they stand to lose. They are embracing risky new technology more quickly and scouting the world for alliances and drug-licensing deals."
Did I read that correctly?
A. Yes.
Q. Okay. And as we just discussed, that was one of Merck's strategies as well; to, quote, develop new drugs. Right?
MR. MORROW: Objection.
A. Yes.
Q. Or find new drugs. Right?

A. Um-hum.
Q. And that's what they did with Propecia. Right?
MR. MORROW: Objection.
A. I'm not sure I understand the question. Could you clarify it, please.
Q. Sure. Merck developed Propecia in the hopes that it would help to backfill some of the loss of revenue from these expiring patents.
A. Merck developed Propecia because it already had the molecule finasteride, and it discovered through research that this product grew hair. That's why it developed the product; to meet an unmathematical need. In meeting unmathematical needs, the company can earn revenue and sustain itself.
Q. Okay. We'll get there in just a minute. But what I want to be clear on is the development of Propecia and the launch of it in early 1998 allowed Merck to sell that drug for male hair loss at a brand rate. Correct?
A. Yes.
Q. Okay. Now, if you see the sentence where it says "still some observers".
A. Yes.

Q. It says, "Still some observers doubt all of this effort will be enough. It can take 15 years to turn a newly created molecule into an improved product with many more failures than successes along the way. Only about one in 250 chemical compounds that go into the laboratory and animal testing ultimately make it to the pharmacy shelves."

Did I read that correctly?

A. Yes.

Q. All right. So at the time that Merck was facing these expiring patents, it had the happy fortuitiveness that it just happened to have a molecule it could distribute in a completely different way for a completely different use. True?

MR. MORROW: Objection.

A. Yes.

Q. Okay. And that molecule then, which became Propecia, allowed it to sell that product at a brand rate throughout the life of the patent. Correct?

A. Correct.

Q. And that was, what, roughly 15 years?

A. Probably.

Q. Okay. So unlike most drugs that Merck's developed, it did not have to go through the 15-year

process to develop Propecia through finding a new chemical compound and then engaging in the R & D it would take to bring that to market. Correct?

MR. MORROW: Object to the form. You can answer.

A. It would have had to do the same level of clinical testing that it would for any new molecule. It -- it could benefit from some of the work that had been done on Proscar, but not all of it.

Q. Right.

A. Because that was a urol -- urological product.

Q. Right. But it didn't take, in fairness, Mr. Howes, 15 years for Propecia to come from idea to sale. Correct?

MR. MORROW: Objection.

A. I don't know how long it took.

Q. Do you know when Merck first identified the need or the potential to be able to use Propecia as a hair replacement drug?

A. No.

Q. Okay. Would it surprise you that that occurred sometime in the mid '90s?

MR. MORROW: Objection.

A. That's entirely possible, sure.
Q. You were at the company when Proscar came online, right?
A. Yes.
Q. Okay. To the best of your knowledge, as you sit here today, nobody was talking about using finasteride as a hair replacement therapy prior to the launch of Proscar, right?
MR. MORROW: Objection.
A. I'm not aware of that.
Q. Okay.
A. I'm not aware that that statement is correct.
Q. You're just not aware of whether it's correct or incorrect?
A. Correct.
Q. Okay.
A. Yes.
Q. All right. So let's assume, for the sake of argument, that the concept of developing a hair loss drug first started to be talked about at Merck sometime in the '90s.
MR. MORROW: Objection.
Q. It's fair to say that that time period from the mid '90s to the launch of Propecia was

not a 15-year time frame. Correct?

MR. MORROW: Objection.

A. I would assume that even if they did not have to do Phase I clinical trials, they would have had to do Phase II and Phase III. And if the product was launched in 1998, it would have been filed maybe at the end of '96. And those trials probably started in 1990, at the latest. So it was the better part of a decade, even with the molecule that had a strong body of scientific data already.

Q. Okay. We'll look at some documents about that a little later on in the deposition. But the bottom line is -- and I think you would agree with this -- that Merck was able to build off of the R & D it did related to Proscar when it started to develop Propecia. Right?

A. Yes.

Q. So it didn't have to go through the complete process.

A. Correct.

Q. Okay. Now, at the time that this drug was being developed, Merck looked at it as a potential blockbuster-type drug. Correct?

MR. MORROW: Objection.

A. Yes.
Q. Tell the jury what a blockbuster drug is.
A. Well, when I first joined the company, that would have been defined as a product that had more than $100 million in sales. Today's definition would probably be more like a billion. And so 1998 may have been somewhere in the middle of that.
Q. So -- but, generally speaking -- and I get your point that the term "blockbuster" and the amount of revenue that's tied to it has evolved over time. Blockbuster drugs are big deals to big pharmaceutical companies, correct?
A. Yes.
Q. And, in fact, big pharmaceutical companies like Merck rely on blockbuster drugs to keep the company afloat. True?
MR. MORROW: Objection.
A. They -- they rely on any first-in-class medication. You've -- you've got to be good at something in order to sustain yourself and continue the operation.
Q. Right. But those blockbuster drugs, in particular, are really what sustains the company so it can go on to do non-blockbuster-type things. Right?

A. Yes.
MR. MORROW: Objection.
Q. That was a yes, right?
A. Yes.
(Deposition Exhibit 229 - Merck Publication titled "The Daily" - MRKP0001704574 through MRKP0001704577 - marked for identification.)
Q. Let me show you what has been marked as Exhibit 229. Can you tell us, sir, is this an internal Merck publication?
A. Yes. It may only be U.S. --
Q. It's --
A. -- but it's a daily publication. Or it was at that point in time.
Q. So I'm assuming that Merck, like most companies, has a way that it communicates information with its employees and staff. Correct?
A. Yes.
Q. And one of the ways it does it is through articles and publications like this. Correct?
A. Correct.
Q. All right. Turn to the third page of the document, which is Bates-numbered MRKP0001704576.
First, just so you know -- have you ever had

your deposition taken before?

A. No.

Q. Okay. So then that code that I just rattled off is probably pretty Greek to you. These are what we call Bates numbers at the bottom. It's just a way for us to track pages. Okay? So I will from time to time refer to these type of codes.

A. (Witness nods head.)

Q. Just as a "go to this page".

A. Yes.

Q. All right. So you're on Bates Page No. 4576. Correct?

A. Correct.

Q. Do you see the column that says "Enthusiasm for Propecia Comes from Many Voices"?

A. Yes.

Q. Okay. Directing your attention to the second paragraph down, there's a quote by ABB Aros Security. Do you see that?

A. Yes.

Q. It says, "This could be a blockbuster. It might take a little while, but you will -- you'll see this as a very high-profile product. Many physicians, for instance, will use this as ammunition to attract

new patients. For many men it will be a very viable treatment."

Did I read that correctly?

A. Yes.

Q. Okay. And then at the bottom of the page, you see the quote from the Wall Street Journal?

A. (No response.)

Q. Bottom of the column.

A. Yes.

Q. It says, "Whatever drawbacks there may be of Propecia, the possibility of combating one of the most common signs of aging in a culture addicted to youthfulness has some analysts predicting that Propecia will become one of the pharmaceutical industry's most successful drugs."

Did I read that correctly?

A. Yes.

Q. Okay. This article is dated January 6th, 1998. True?

A. Yes.

Q. This is on the eve of the launch of Propecia. Correct?

A. Correct.

Q. So at the time that the product is being

launched, the expectation in the company, as well as on the street, was that this drug was going to be a big deal to Merck.

A. I -- I don't know if that was the expectation in the company. It's clearly the external expectation. Analysts and -- and others.

Q. One of the ways those analysts got that expectation was because Merck promotes its products. Correct?

MR. MORROW: Objection.

Q. Right?

A. Merck does promote its products, yes.

Q. And so these analysts didn't just pull this information out of thin air, did they?

A. No. But, also, none of them had seen the label of the product either.

Q. Okay. So the point being that when analysts are reporting on what they anticipate a particular pharmaceutical will do, how much it will make in terms of gross revenue, some of that information was coming from the pharmaceutical company itself. Correct?

A. True.

Q. So, in other words, ABB Aros Security and the Wall Street Journal was getting some of its information

related to the likely success of Propecia from Merck directly.

MR. MORROW: Objection.

A. Likely, yes.

Q. Okay. Turn, if you would, to the first page of the document.

A. (Witness complies.)

Q. Now, one of the reasons why Merck thought that this product was going to be particularly successful is because there was a large, untapped market of men who might actually buy Propecia. Correct?

A. Yes.

Q. In fact, if you look at the first column, the article reports, about two-thirds of the way down, "with a target audience". Do you see that?

A. On the left side or the --

Q. On the far left side, first column.

A. Yes.

Q. "With a target audience of 33 million U.S. men, analysts hold high hopes for Propecia."

Did I read that correctly?

A. Yes.

Q. Okay. So Merck saw a large opportunity with

lots and lots of potential consumers or customers to buy this particular product that, really, nobody else was in this area at the time. Correct?

A. Correct.

Q. Okay. And it thought at the time that if it could capture a significant portion of those 33 million men, it could, in fact, develop a blockbuster drug. Correct?

A. Yes.

Q. Turn to the next page, if you will.

A. (Witness complies.)

Q. And direct your attention to the far left-hand column. Third paragraph down, starting with "even a scarcity". Do you see that?

A. Um-hum.

Q. It says, "Even with a scarcity of proven remedies, men spend some $1 billion annually on treatment."

Did I read that correctly?

A. Yes.

Q. So at the time that Merck was developing Propecia and was getting ready to launch it, it knew that sales related to hair replacement therapy, generally, in the U.S. market exceeded a billion

dollars annually. Correct?

A. Yes.

Q. So it saw a huge opportunity for potential revenue within that market. Correct?

A. Correct.

Q. And if you go down to the next paragraph, there's a quote by Mr. Casola, who was your subordinate at this time, correct?

A. Not at this time, but he was.

Q. I'm sorry. You're right.

A. Six months later.

Q. I'm sorry. You're correct. At this point he was actually -- you weren't working on this particular project.

A. Correct.

Q. Okay. So he was in charge of it from a marketing standpoint?

A. Yes.

Q. Okay. So Mr. Casola states, quote, "There is definitely a large group of men searching for help. We just need to communicate the benefits of Propecia to them and motivate them to see their physicians."

Did I read that correctly?

A. Yes.

Q. All right. So you knew internally that if these sexual adverse events were prolonged or lengthened or never went away, that that would be something that would impact sales in a negative way. Right?

MR. MORROW: Objection.

A. Yes.

(Deposition Exhibit 238 - Report - MRKP0001787636 through MRKP0001787644 - marked for identification.)

Q. Let me show you what I have marked as Exhibit 238.

MR. MORROW: I'm sorry. 238?

MR. BECKER: 8.

Q. Do you have that documents there in front of you, sir?

A. Yes.

Q. Okay. It's a document that is -- the subject is entitled "Evaluation of the 1998 Direct-to-Consumer Advertising Campaign for Propecia, End-of-Year Report on the Consumer Awareness and Action Study" dated March 15, 1999. Do you see that?

A. Yes.

Q. And you are listed in the distribution list.

Correct?

A. Yes.

Q. Okay. Let me direct your attention to the top of the page. Do you see where it says, "This is an information report. Please destroy by March 1st, 2001. Available from the MIC after this date."?

Do you see that there?

A. Yes.

Q. Okay. What is the MIC?

A. I believe it stands for Marketing Information Center.

Q. Okay. So the author of this -- well, let me ask you this: Was it company policy that this type of an internal market analysis be destroyed by its recipients?

A. I don't know.

Q. Do you know whether or not Merck had a document destruction policy?

A. It has a records retention policy.

Q. Okay. Do you know, were these type of documents slated for destruction within that retention policy?

A. I don't know.

Q. Okay.

A. I mean, it wasn't -- it was obviously retained in a repository.

Q. Do you know how -- were -- were emails subject to that document retention policy?

A. I don't know.

Q. Okay. Do you remember if you saved a copy of this document? Or would you have destroyed it per these instructions?

A. I don't know.

Q. All right. You had an understanding at the time --

A. The objective is that it's -- it's proprietary market research information, and you don't want it ending up in an analyst report. Whatever it is on any product. It's proprietary. So that's why they want to keep it in one location and not have it lying around people's desks, and when people leave the company, they join -- leave Merck, go join Pfizer, they take all this stuff with them. That's why they have policies like that.

Q. So that's the point. It was intended to be only for internal Merck use. Correct?

A. Yes.

Q. And the vast majority of the copies were to

be destroyed. Right?

A. Yes.

Q. All right. So let me direct your attention to the first page of the document titled "Summary". Do you see that?

A. Yes.

Q. Directing you to the third -- sorry -- fourth and fifth bullet point, the fifth one says, "Sexual side effects and side effects associated with pregnant women (women not handling Propecia) are the predominant side effects recalled by respondents."

Did I read that correctly?

A. Yes.

Q. And then the bullet point above that says, "40 percent of those men aware of Propecia are aware of side effects associated with taking the product. Of those, side effects would prevent 50 percent of the men from taking the product." Correct?

A. Yes.

Q. Okay. So 40 percent of the -- of the mean who had an understanding or a brand awareness of Propecia were aware of the fact that sexual side effects could occur if they took the drug. Right?

A. Yes.

Q. And of those people who were aware, 50 percent said I'm not touching it. Right?

A. Yes.

Q. Okay. So, in other words, 20 percent of the guys who had awareness of Propecia said, we are absolutely never taking this thing. Right?

A. Yes.

Q. All right. And at the time that they had that view of the drug, there was no warning for persistent to permanent erectile or sexual dysfunction. Correct?

A. Correct.

Q. Does it stand to reason that if 20 percent of the men who were in the pool of guys who could use the drug would not touch it, recognizing that the symptoms could go away, that that percentage would have gone even higher if they thought that use of the drug could cause permanent, persistent problems for them?

MR. MORROW: Object to the form.

A. Yes. The converse is also true, though.

Q. Turn to -- turn to Page 7641.

A. (Witness complies.)

Q. And, specifically, I want to direct you to the section "Awareness of Side Effects". Do you see

the heading there, "Awareness of Side Effects"?

A. Yes.

Q. There's a figure under that, Figure 5, "Side Effects, Components, Total Ad Recall".

A. Yes.

Q. And it starts out in -- at the bottom June and goes to late December on the -- on the -- on the lower axis. Do you --

A. Yes.

Q. -- see that?

A. Yes.

Q. And then on the -- on the left side tracks the -- a percentage number. Right?

A. Okay.

Q. Do you see that there?

A. Yes.

Q. Okay. And then the first graph is the graph of people who were aware of sexual side effects. Correct?

A. The first bar?

Q. The first bar.

A. Okay.

Q. And if you look at that, you basically -- well, describe for us what this chart is laying out.

A. I -- I can't read the labeling on the bars.
Q. Okay. So -- I have that same problem. These are relatively new.
(Discussion held off the record.)
Q. Okay. Here's how I read it: The first bullet point is "sexual side effects". Do you see that?
A. Yes.
Q. The second graph is "pregnant women shouldn't handle". The black --
A. Yes.
Q. And on the clear one --
A. That one goes up over time.
Q. -- is birth defects to unborn children. And general warning has a side effect, health warning. Those are the bars that are denoted.
A. Yes.
Q. Do you see that there? So, basically, this chart is graphing the number of men in the focus groups you looked at who had a recognition of the brand Propecia, along with certain side effects that were disclosed in the labeling. Correct?
A. Yes.
Q. Okay. And if you turn to the next page, it

tracks -- the Figure 6 indicates, "Would side effects prevent you from using Propecia?" Do you see that?

A. Yes.

Q. Okay. And then it's "yes", "no", "don't know". Do you see that?

A. Um-hum.

Q. And the lowest that "no" answer ever -- or "yes" answer ever appears to be is just below 40 percent baseline. Do you see that?

A. Yes.

Q. And then every other month thereafter hovers around the 50 percent or higher number. Correct?

A. Yes.

Q. And that led to the conclusion that if you were aware of sexual side effects, those men who were aware of it, around half would not take the drug.

A. Right.

Q. Turn to Page --

A. And it wasn't just the sexual side effects. It was the combination of the two; the fact that it was dangerous to be even touched by a female of child-bearing years, that affects men's behavior as well as women's -- I mean, women don't use this product.

Q. Right.
A. But they didn't want it in the house.
Q. But this chart charts it out specifically for -- strike that. I -- I hear what you're saying. Fair enough.
Go to Page 87644; the last page of the document.
A. (Witness complies.)
Q. Do you see the heading that says "Next Step"?
A. Yes.
Q. It says, "Fear of side effects is one barrier of action that the TBG is interested in better understanding. A & A questions have been revised to understand the role of side effects in preventing men from acting and how the -- and how the product in DTC campaign can be revised to minimize these concerns."
Do you see that there?
A. Yes.
Q. So the walkaway from this was that we understand we have a problem with sexual side effects, and we, as a company, have to figure out how to address that.
A. Yes.
Q. Okay. That never really worked, did it?