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MERCK SHARP & DOHME

To: Swedish Medical Products Agency (MPA)
Ms Anna Litzen
Dr Jolanta Gulbinovic
Dr Gunilla Sjölin-Forsberg

Cc: The National Competent Authorities in:
Austria, Denmark, Finland, France,
Germany, Greece, Iceland, Italy,
Luxembourg, Netherlands, Portugal, Spain

Brussels, June 18th, 2007

Subject: **PROPECIA (finasteride) 1 mg film-coated tablets**
CAPIPRO (finasteride) 1 mg film-coated tablets
Response to Assessment Report on PSUR
Erectile dysfunction after cessation of treatment – additional data

Dear Sir/Madam,

In the recent Assessment Report for the Propecia PSUR, covering the period from November 7th 2005 to November 6th, 2006, MSD was requested to submit a type II variation to add the term 'Abnormal liver function tests' in section 4.8 of the SPC and to include information on the persistence of erectile dysfunction after cessation of treatment in section 4.4 of the SPC.

This request was further discussed during a meeting held between MSD and the MPA on the 4th of June 2007. The MPA concurred that the Type II variation on abnormal liver function tests does not need to be filed at this time, pending their review of additional information to be provided MSD by July 18, 2007.

With regards to the MPA request to update section 4.4 of the SPC with information on the persistence of erectile dysfunction after cessation of treatment, MSD wishes to confirm our position that the pre-clinical, clinical and post-marketing data do not support inclusion of precautionary text in the SPC. A response document addressing the comments made in the Assessment Report is submitted herewith.

These responses are submitted electronically to the RMS and CMS (see attached list). Hard copies are available on request.

Do not hesitate to contact the undersigned should you require further information.

Yours faithfully,

EXHIBIT
214
5-19-16
P. FRANK

Emilie Niedercorn

Cover letter

PROPECIA (finasteride 1 mg)
Responses to Comments in PSUR Assessment Report
Reversibility of Male Reproductive System Disorders

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Response to Comments in PSUR Assessment Report
Reversibility of Male Reproductive System Disorders
PROPECIA (finasteride 1 mg)

In the Assessment Report to the PROPECIA (finasteride 1 mg) PSUR # 19, covering the period from 07NOV05 to 06NOV06, the MPA requested that a Type II variation be filed to add information on persistence of erectile dysfunction following cessation of treatment to Section 4.4, Special warnings and special precautions for use of the SPC. The MPA made comments with regard to potential lack of clarity around the clinical data in this regard and also cited a publication as supportive of the requested labeling change. With this response, MSD wishes to address the comments made in the Assessment Report and confirm our position that the pre-clinical, clinical and post-marketing data do not support inclusion of precautionary text in the SPC.

Pre-Clinical

Finasteride has been extensively studied in male rats and rabbits as part of the reproductive toxicity evaluation. The details from the male rat studies were published in a peer-reviewed journal by Wise et al (1991) and Cukierski et al (1991). The results from extensive evaluation of male fertility have demonstrated that finasteride has no effect on indices of mating (mean day of mating and mating incidence). The mating incidence [mated females/females cohabited (x100)] was similar to vehicle control groups irrespective of the dose or duration of treatment. Furthermore, finasteride had no effect on mating performance, irrespective of the age (sexually immature vs. mature rats) when the treatment was initiated. Thus, in sexually immature male rats, inhibition of DHT levels with finasteride had no adverse effect on sexual maturity or the ability of the males to mate. Similarly, chronic (up to 6 months) administration of finasteride to sexually mature rats had no effect on the mating indices. The dose studied (80 mg/kg/day) in rats resulted in high systemic exposure and the dose was greater than 100 fold above the anticipated pharmacological effect on the target tissue (prostate). Similarly, in rabbits, administration of a high dose (80 mg/kg/day) of finasteride for 3 months had no effect on mating indices. The above observations support the conclusion that long-term administration of finasteride has no adverse effect on penile erectile tissue in rats and rabbits.

Since finasteride has been shown to be very selective in its desired pharmacological effect (5α-reductase inhibition) with no androgenic or antiandrogenic effects, there is no scientific basis for mechanistic explanation of erectile dysfunction in either laboratory animals or in men treated with finasteride. Although, Shen et al. (2003) showed that castration (total androgen ablation) in rats resulted in a statistically ($P<0.05$) significant effect on thickness of penile tunica albuginea, there was no significant ($P>0.05$) effect in finasteride-treated rats. They described qualitative changes based only on scanning electron microscopic observations. Their description of qualitative differences in erectile tissue in finasteride-treated animals compared to controls is inconsistent with functional observations in fertility studies in rats and rabbits. Furthermore, in fertility studies, animals received very high does of finasteride (80 mg/kg/day) for 3 to 6 months. This was adequate to completely inhibit DHT levels with no effect on T levels. In contrast, in the study by Shen et al. (2003), the rats were treated for only one month at a low dose

(4.5 mg/kg/day) that resulted in only 50% inhibition of DHT with no apparent differences in serum T levels. Therefore, the study by Shen et al. (2003) fails to demonstrate that DHT is critical for structural and functional integrity of penile erectile tissue.

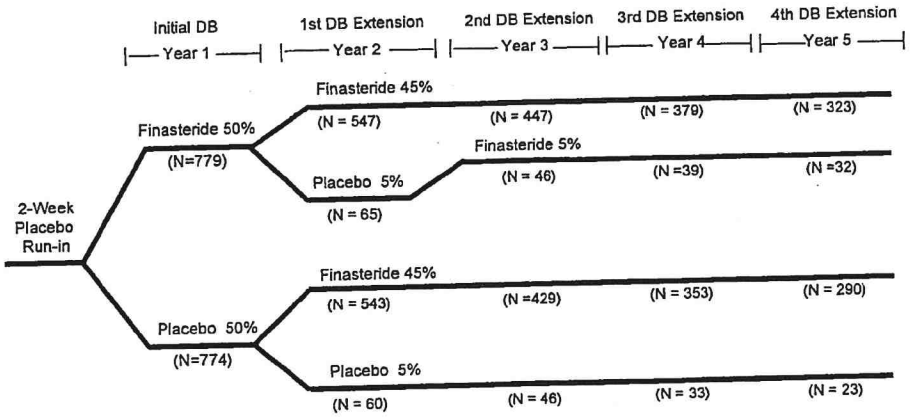
The preclinical data support the conclusion that finasteride has no adverse effect on penile erectile tissue.

Clinical

The Phase III clinical program for PROPECIA consisted of 3 studies. Two studies (087-US and 089-International) in men 18-41 years of age with predominately vertex hair loss share a common design and provide the most comprehensive safety data. Both studies were double-blind, randomized, placebo-controlled, multicenter, 1-year studies. After a 2-week placebo run-in period, patients were randomized 1:1 to finasteride 1 mg/day or placebo for 12 months. These 1-year studies were followed by four, 1-year, double-blind, randomized, placebo-controlled, multicenter extension studies. As predefined in the data analysis plan for the initial 12-month studies and the data analysis sections for each of the extension studies, data from the US (087) and the International (089) studies were combined for analysis.

In the initial 12-month studies, 1553 patients with male pattern hair loss were randomized to 1 of 4 treatment groups, dictating patient allocation to treatment through a total of up to 5 years of controlled clinical trial observation (Figure 1). During the first year, patients received finasteride 1 mg (779 patients) or placebo tablets (774 patients) orally per day. The number of patients who entered the first, second, third and fourth extensions on treatment with finasteride or placebo is shown in Figure 1.

Figure 1
Treatment Assignments in Each Year of the Phase III Pivotal Studies



During the initial studies and their extensions, investigators collected patient-reported AE information during each clinic visit. Investigators rated AEs by severity, intensity, seriousness, and drug relationship according to one of the following five descriptions: definitely not, probably not, possibly, probably, and definitely drug-related; a drug-related AE was thus defined as being considered as possibly, probably, or definitely drug-related. Sexual AEs were defined as untoward effects on sexual function and included primarily changes in libido, ejaculation disorders, and erectile dysfunction.

To document resolution of sexual AEs once therapy with finasteride was discontinued, patients who discontinued from the study due to a drug-related sexual AE were contacted after discontinuation to obtain information on the status of the AE. Over the course of the 5-year studies, 72 men receiving finasteride at the time of AE occurrence reported sexual adverse experiences considered drug-related by the investigator. Of these 72 men, 24 discontinued from the study because of the AE, while 48 remained in the study on treatment; of these 48 men, 32 (67%) reported resolution of their sexual adverse experience while continuing on treatment with finasteride. Of the 24 men who discontinued due to a drug-related sexual AE, follow-up information is available for 23 (96%). Of these 23 men, 22 reported resolution of their sexual adverse experience; one patient reported the adverse experience still present 6 months post-discontinuation, but no further follow-up information is available.

Thus, the 5-year controlled clinical trial experience with finasteride in the Phase III Pivotal studies and their four, 1-year, double-blind extensions studies demonstrated that for 71 men who experienced sexual AEs considered by the investigator as related to therapy with finasteride and for whom outcome data are available, the adverse experience resolved for 22/23 (96%) who discontinued therapy and for 32/48 (67%) who remained on therapy with finasteride.

In the third Phase III study, the 1-year, double-blind, placebo-controlled randomized Phase III study in 326 men with predominately frontal male pattern hair loss (092), drug-related sexual AEs were reported by an equal proportion of patients in each treatment group (3 patients in each treatment group, or 1.8% and 1.9% of patients in the finasteride and placebo groups, respectively), and no patient discontinued from the study due to a sexual AE.

Taken together, the data from the Phase III clinical studies (087, 089, 092) demonstrate that for men with drug-related sexual adverse experiences, the AE resolves in those who discontinue treatment with finasteride and in most who continue on therapy.

Post-Marketing

Although there is a significant amount of post-marketing data for finasteride, spontaneous reporting systems can only produce signals of potential cause-effect relationships because the information is most often incomplete and the systems are sensitive to multiple biases

including underreporting, length of time a product has been on the market, country, reporting environment, and quality of the data.

A detailed review of 617 post-marketing reports of erectile dysfunction with finasteride was provided in the last PSUR (cut off date 06-Nov-2006). In these spontaneous reports the majority of reports, 93%, were non-serious. In reports where an outcome was provided half described an outcome of recovered/recovering at the time the report was received. In reports where the events persisted, at the time of the report, many were insufficient for evaluation and/or reporting continuing finasteride therapy. Many reports described concurrent conditions, and/or medical histories which may have contributed to the patient's experiences. Only 75 reports have been received where patients described an adverse experience which persisted after discontinuing therapy with finasteride, at the time of the report. The majority of the reports lacked specific information to allow for further evaluation. No information was provided about the duration of the event following the discontinuation of finasteride and/or no information of a detailed urologic work up was provided.

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In most of the 617 reports the information was provided shortly after the onset of the adverse experience and despite attempts to obtain follow up information, in accordance with the Company's standard procedures to obtain follow up, no further information was provided. In an additional follow up review of these reports, only 15 reports had received any new clinical information from 06-Nov-2006 to 07-Jun-2007. None of these reports reported a change in outcome of the event.

Conclusion

Finasteride has been studied extensively in preclinical species as part of the reproductive toxicity evaluation. In these studies, inhibition of DHT levels with finasteride had no effect on sexual maturity or the ability of the males to mate. Although the Assessor has cited a study by Shen et al. to support that there may be a mechanistic basis for erectile dysfunction in association with finasteride, there are multiple deficiencies with the paper and they failed to demonstrate that DHT is critical for structural and functional integrity of penile erectile tissue. In addition, since finasteride has been shown to be very selective in its desired pharmacological with no androgenic or antiandrogenic effects, there is no scientific basis for mechanistic explanation of erectile dysfunction in either laboratory animals or in men treated with finasteride.

As noted by the assessor, some of the post-marketing reports in which patients described a sexual adverse experience that persisted after discontinuing therapy with finasteride lacked specific information to allow further evaluation. As noted above, this lack of follow-up is due to limitations of a spontaneous reporting system. Information reported to a spontaneous post-marketing surveillance system is most often incomplete and the systems are sensitive to multiple biases including underreporting, length of time a product has been on the market, country, reporting environment, and quality of the data. Follow-up data received in a spontaneous reporting system is reliant upon the voluntary

compliance of the reporter to respond to solicitation for additional information regarding the AE. Follow-up information in a post-marketing reporting system is a snapshot in time and without continued investigation cannot be used to draw definitive conclusions.

Limitations also exist with regard to the ability to obtain comprehensive follow up data on patients who discontinue from clinical trials; however, in the case of the long-term controlled clinical trials with PROPECIA, follow-up information on persistence or resolution of sexual AEs following cessation of treatment is extremely complete and provides a superior assessment compared to that possible through spontaneous AE collection.

In the 5-year controlled Phase III clinical trial experience, 72 men experienced a sexual AE that was considered drug related by the investigator. Only 24 of these men discontinued therapy with finasteride due to the AE. Of these, follow up information on resolution is available in 23 men and in 22 (96%) of these men, the AE resolved following discontinuation of therapy. A single report of the continued presence of a sexual AE six months following discontinuation of finasteride exists in the clinical database. No follow up data is available beyond this 6-month timepoint, so an ultimate assessment regarding persistence or resolution cannot be made. Nevertheless, the preponderance of data support that sexual AEs reported in men taking finasteride resolve when therapy is discontinued. Furthermore, in men who choose to continue therapy despite sexual AEs, many of the AEs resolve while on drug.

In summary, a small number of spontaneous post-marketing AE reports of persistent sexual dysfunction exist which in the absence of additional follow-up information appear to conflict with data from controlled clinical trials. This is likely not unique to this AE or to finasteride specifically and simply points to the limitations of a post-marketing surveillance system. Post-marketing surveillance is a signal detection tool and should not be used to qualify and/or precisely quantify cause and effect relationships between drugs and AEs if better data from clinical studies are available. Thus the data from the clinical trials with finasteride should be considered over that of reports received from the post-marketing environment.

Section 4.8, Undesirable Effects, of the current SPC indicates the incidence of sexual AEs (and others) reported in clinical trials. The statement that undesirable effects have usually been transient during treatment or resolved upon discontinuation is accurate as regards the sexual AEs (and others included in the SPC). The pre-clinical data are predictive of what was seen in the clinical trials, in that no mechanism for lack of resolution of sexual AEs can be elucidated from the extensive preclinical database. The post-marketing data are subject to obvious limitations; however, despite the fact that not every outcome can be accounted for, they are generally supportive of the clinical data as well. Thus, the Sponsor considers the current SPC for PROPECIA to be appropriate and reflective of the available data and does not support inclusion of precautionary text in the SPC regarding persistence of erectile dysfunction following discontinuation of treatment.

Response to Comments in PSUR Assessment Report
Reversibility of Male Reproductive System Disorders
PROPECIA (finasteride 1 mg)