LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

PREL RENEWAL ASSESSMENT REPORT

Propecia and Capipro

Invented name of the pharmaceutical product in the Reference Member State	**Propecia and Capipro**
Name of the active substance	Finasteride
Pharmacotherapeutic classification (ATC code)	D11AX
Pharmaceutical form and strength	Film-coated tablets 1 mg
PSUR-period	7 Nov 2002 to 18 Aug 2007
MAH	Merck Sharp & Dohme B.V, Haarlem, Netherlands
European Procedure number	SE/H/158-159/01/R/002
Member States concerned	**Propecia**: AT, DE, DK, EL, ES, FI, FR, IS, IT, LU, NL and PT **Capipro**: DE, EL, FR and PT
Clinical Assessor	Jolanta Gulbinovic
Product Information Assessor	Nora Åhlander
Quality Assessor, GMP	Peter Aullo
Quality Assessor	Lena Hansson
Project Manager	Helena Malm

Procedure Start Date	10 December 2007
Date of Preliminary Renewal Assessment Report (day 40)	19 January 2008
Deadline for comment (Day 55) to RMS	3 February 2008
Evaluation completed or Clockstop	7/8 February 2008
Procedure Restart Date	
Date of Final Renewal Assessment Report (Day 60)	
Deadline for comments to RMS (Day 85)	
End of Procedure (Day 90)	
Common renewal date	17 April 2008

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1. Introduction

This application concerns a renewal of the Marketing Authorisation for Propecia (finasteride, 1 mg). It contained administrative documentation, documentation addressing pharmaceutical quality, a clinical overview, and a Summary Bridging report that summarises information from 07-Nov-2002 to 18-Aug-2007. In addition, all PSURs were included into the application. The PSURs covering period from 07-Nov-2002 to 06-Nov-2006 have been assessed earlier. The last 6-month PSUR (07-Nov-2006 to 06-May-2007) and an addendum report (07-May-2007 to 18-Aug-2007) will be discussed in this report together with the overall safety data.

Propecia is indicated for early stages of androgenetic alopecia in men. Propecia stabilizes the process of androgenetic alopecia in men 18-41 years of age.

In the last PSUR (07-Nov-2005 to 06-Nov-2006) assessment report, the MAH was requested to update section 4.8 of the SPC with abnormal liver function tests, and include information on possible persistence on erectile dysfunction after discontinuation of Propecia in section 4.4. However, the MAH refused to submit a type II variation and has submitted new cumulative reviews on these issues which are assessed in this report.

Additionally, the MAH was requested to present cumulative reviews of cardiac disorders, off-label use in children and female patients and lack of efficacy. These cumulative reviews are also assessed in this report.

2. Worldwide Market Authorization Status

At the time of this Summary Bridging Report, finasteride, 1 and 0.2 mg tablets, MSD had been registered and approved in 63 countries.

Registration of 0.2 mg Tablet
A local study was conducted to support the registration of Propecia in Japan. As required by the Agency, the study included both the 0.2 and 1 mg dose strengths of finasteride. Following review of the efficacy and safety data from this study, the agency requested the registration of both the 0.2 and 1 mg dose strengths. The recommended starting dose is 0.2 mg, although patients can initiate therapy on the 1 mg dose or increase the dosage from 0.2 mg to 1 mg, as directed by a physician. No other country has the 0.2 mg dose strength registered.

3. Regulatory authority or MAH actions taken for safety reasons

During the reporting period of this Summary Bridging Report there have been no regulatory or manufacturer actions related to finasteride, 1 mg and 0.2 mg tablets, MSD that resulted in marketing authorization withdrawal or suspension, failure to obtain marketing authorization renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population, or pharmaceutical changes for safety reasons.

4. Changes to Reference Safety Information

The Worldwide Product Circular (WPC) is the Company Core Data Sheet (CCDS) which contains the Company Core Safety Information (CCSI), indications, dosage, pharmacology, and other product information. This information is based on the Company's ongoing review of the safety profile of finasteride, 1 and 0.2 mg tablets, MSD.

During the reporting period of this Summary Bridging Report, there were no safety related updates to the CCDS for finasteride, 1 and 0.2 mg, MSD.

5. Patient exposure/Quantities dispensed worldwide

5.1 Clinical Trials

The number of patients who were enrolled in Merck-sponsored clinical trials between 07-Nov-2002 to 18-Aug-2007 and who were treated with finasteride, 1 and 0.2 mg tablets, MSD was approximately 473.

5.2 Market Experience

The worldwide distribution of finasteride, 1 and 0.2 mg, MSD between 07-Nov-2002 to 18-Aug-2007 is summarized in Table 1. Patient-years of treatment are also provided based on the assumption of 1 tablet daily, either 1 mg or 0.2 mg tablet.

Table 1: Market Experience

Strength	07-Nov-2002 to 18-Aug-2007[1]		Market Launch (11-Sep-1997) to 18 Aug-2007[2]	
	Distribution (tablets)	Patient-Years of treatment	Distribution (tablets)	Patient-Years of treatment
1 mg tablets	985,852,700	2,700,966	1,712,543,154	4,691,899
0.2 mg tablets	3,073,212	8,420	3,073,212	8,420
Total	**988,925,912**	**2,709,386**	**1,715,616,366**	**4,700,319**

[1] This estimate of patient exposure for this period is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated for the period from 01-Nov-2002 to 31-Jul-2007 rather than for the period 07-Nov-2002 to 18-Aug-2007.
[2] This estimate of patient exposure for this period is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated for the period from market launch to 31-Jul-2007 rather than for the period to 18-Aug-2007.

6. Presentation of Individual Case Histories/Adverse drug reactions

Only the reports where Propecia was considered the primary suspected therapy were included in the PSURs

Assessor's comment:
The consideration of the MAH to include only reports where Propecia was primary suspected drug does not comply with the Volume 9A. The MAH should present a total number of cases were Propecia was suspected therapy. Line listing of not included cases should be also provided.

Summary Bridging Report
Cumulative summary tabulations of all spontaneous ADRs and ADRs from clinical studies, including serious and non-serious unlisted, serious and non-serious listed, were provided. No specific case histories were presented and discussed.

Based on the data from the PSUR (07-Nov-2006 to 06-May-2007) and addendum PSUR, since market introduction until 18-Aug-2007, 5152 spontaneous reports and 5 study reports meeting PSUR criteria were received, including 519 reports with serious events.

6-month PSUR (07-Nov-2006 to 06-May-2007)

During the period of this PSUR, 544 spontaneous reports and no study reports meeting PSUR criteria were received. Of these, 44 reports were with serious events (34 unlisted), 388 reports with unlisted non-serious and 112 reports with listed non-serious.

The most frequently reported serious unlisted events were hepatic function abnormal (n=3), epistaxis (n=2), myocardial infarction (n=2), blood CPK increased (n=2), accidental intake by child (n=2).

Short summaries of cases with serious unlisted events were provided.

Cases with non-serious unlisted events were not discussed.

PSUR addendum report (07-May-2007 to 18-Aug-2007)
During the PSUR addendum period, 299 spontaneous reports and 1 study report meeting PSUR criteria were received. Of these, 26 reports were with serious events, 192 reports with unlisted non-serious and 82 reports with listed non-serious.

No case histories were presented in the addendum PSUR.

There were several safety issues of concern for which cumulative reviews were provided. They are discussed in section 9.

7. Studies

7.1 Newly Analyzed Studies

During the reporting period of this Summary Bridging Report, there were no newly analyzed studies that contained important, new safety information for finasteride, 1 and 0.2 mg, MSD.

7.2 Targeted New Safety Studies

During the reporting period of this Summary Bridging Report, there were no targeted safety studies that were initiated, ongoing, or have been completed but not yet analyzed for finasteride, 1 and 0.2 mg, MSD.

7.3 Published Safety Studies

During the reporting period of this Summary Bridging Report, the following published safety studies that described new and potentially important safety information for finasteride, 1 and 0.2 mg, MSD were discussed in the indicated PSURs:

07-Nov-2002 – 06-May-2003

- **Lin J. H. and Chen W. C. Finasteride in the Treatment of Taiwanese Men With Androgenetic Alopecia: A 12-Month Open-Label Study. Kaohsiung J Med Sci 2002; 18(8): 379-385.**

07-May-2004 – 06-Nov-2004

- **Prostate Cancer Prevention Trial (PCPT) and Propecia:** A summary of the published results of this trial were originally included in Section 7.0 of the Proscar PSUR # 23 (timeframe 07-May-2003 to 06-Nov-2003). The increase in the prevalence of high-grade prostate cancer was observed in the PROSCAR group. The relevance of these findings with finasteride 5 mg to the use of finasteride 1 mg in men for treatment of male pattern hair loss is unknown.

- **Kawashima M, Hayashi N, Igarashi A, Kitahara H, Maeguchi M, Mizuno A, Murata Y, Nogita T, Toda K, Tsuboi R, Ueki R, Yamada M, Yamazaki M, Matsuda T, Natsumeda Y, Takahashi K**

and Harada S. Finasteride in the treatment of Japanese men with male pattern hair loss. Eur J Dermatol 2004; 14(4): 247-254.

8. Other Information

8.1 Efficacy-Related Information

During the reporting period of 07-Nov-2006 to 06-May-2007, reports of lack of efficacy for finasteride, 1 and 0.2 mg, MSD, received by the Company did not suggest a hazard to the treated population.

Cumulative review on lack of efficacy was provided. From product launch (11-Sep-1997) through 18-Aug-2007, a total of 665 spontaneous reports of lack of efficacy were identified: 19 were serious report; the remaining 646 reports were non-serious. The majority of the reports was received from the USA (n=381), Japan (n=159), Germany (n=31), Canada (n=22), and the UK (n=19).

The 665 reports were stratified according to the time to onset of the reported lack of efficacy event in relation to the start of Propecia therapy. There were 171 reports where lack of efficacy developed within the first 3 months of initiating therapy with Propecia; 82 reports where the time to onset of the reported lack of efficacy developed between 3 month and 6 months after the initiation of therapy with Propecia; 145 reports where the time to onset of the reported lack of efficacy was > than 6 months after the initiation of therapy with Propecia, and 266 reports where the time to onset of the reported event was "unknown" or not able to be calculated due to missing information.

Concurrent conditions, medical histories and concomitant therapies that might have contributed to hear loss were reported in 240, 57, and 384 reports, respectively.

The MAH stated that based on clinical trial data, it is clear that 15-20% of patients will not respond to therapy with finasteride 1 mg and may experience continued hair loss. This information is already adequately conveyed in the product information.

The Company considers the current labeling to be appropriate and reflective of the extensive data available on finasteride.

Assessor's comment:
A total of 665 reports of lack of efficacy were identified. A substantial number of reports were from Japan, where the drug was approved quite recently and is under specific monitoring according to the specific requirements for the new drugs.

It is stated in the SPC that generally 3 to 6 months of daily treatment are required before evidence of stabilisation of hair loss can be expected. Therefore the case reports where TTO of lack of efficacy is shorter than 6 months should be interpreted cautiously.

Cases with lack of efficacy should be further monitored.

8.2 Late-Breaking Information

There was no important or new late-breaking information that would alter the currently known safety profile as described in the current CCDS of finasteride, 1 and 0.2 mg, MSD.

9. Overall Safety Evaluation

9.1 Safety issues of specific interest

Several safety concerns were discussed in the previous PSURs and the update to the SPC was requested. This concerned abnormal hepatic tests and persistence of erectile dysfunction. However, the MAH was rather reluctant to the requests of the RMS and submitted the new cumulative reviews of issues of interest instead.

Abnormal liver function tests

In response to the assessment report on PSUR (7-Nov-2005 – 6-Nov-2007), the MAH submitted two separate reviews of cases with increased hepatic enzymes for Propecia (finasteride, 1 mg and 2 mg), and Proscar (finasteride 5 mg).

The WAES database was searched for spontaneous reports mapping to the MedDRA preferred terms of liver function test abnormality in patients treated with finasteride received from HCPs, including regulatory agencies, from product launch (28-Apr-1992, Proscar; 11-Sep-1997, Propecia) through 31-Mar-2007. A total of 356 spontaneous reports were identified from this search. Forty-four of the 356 spontaneous reports identified met the regulatory criteria for a serious report; the remaining 312 reports were non-serious.

There were 228 spontaneous reports (19 serious, 209 non-serious) with primary therapy identified as Propecia 1 mg and 0.2 mg tablet, and 128 spontaneous reports (25 serious, 103 non-serious) with primary therapy identified as Proscar 5 mg tablet.

Propecia 1 mg, 0.2 mg

The majority of reports of abnormal hepatic function tests were received from the USA (67), Japan (58), Germany (35), France (17), Australia (15), and Spain (10).

150 reports concerned patients from 18 to 64 years of age. Age was not provided in 77 reports.

The 228 reports were stratified according to the time to onset of the reported liver function test abnormality in relation to the start of Propecia therapy (Table 2). There were:
• 18 reports where liver function test abnormality developed within the first month of therapy with Propecia
• 85 reports where the time to onset of the reported liver function test abnormality developed between 1 month and 1 year after the initiation of therapy with Propecia
• 30 reports where the time to onset of the reported liver function test abnormality was > than 1 year after the initiation of therapy with Propecia, and
• 95 reports where the time to onset of the reported event was "unknown" or not able to be calculated due to missing information.

Table 2: Distribution of the reports for Propecia with regard to TTO and information provided

TTO	Reports with limited information	Reports with confounding factors	Reports with clinical details and without confounders	Total
≤1 month	8	9	1	18
>1 month - ≤ 1 year	53	17	15	85
> 1 year	15	8	7	30
Unknown	76	15	4	95

There were several reports (not limited to the presented below) reporting positive re-challenge or de-challenge:

WAES 00056212 described a 39 year-old male who experienced increased GGT 250 IU/L and ALT 80 IU/L levels approximately 5 months after starting therapy with Propecia. Research of hepatitis A, B, C antibodies was negative. Therapy was interrupted and GGT (142 IU/L), ALT improved. Therapy with Propecia was restarted and GGT (212 IU/L) and ALT increased again (value not reported). CT scan of the liver was normal. Hepatitis C RNA test was negative. Propecia was discontinued and the patient recovered.

WAES 0204FRA00041 described a 27 year-old male on concomitant topical minoxidil who experienced increased transaminases approximately 3 months after initiating therapy with Propecia: ALT 91 IU/L, AST 54 IU/L, GGT 113 IU/L (normal values not provided). Hepatitis A, B, C serology was negative. Therapy was discontinued and the patient recovered.

WAES 0204DEU00233 described a 31 year-old non-smoking male with no history of alcohol use on no concomitant therapy, who 10 months after starting therapy with Propecia reported increased serum cholesterol (261 mg/dl), LDL cholesterol (194 mg), and ALT 27 U/L (normal ALT 0-22 U/L). AST, AP and tBili reported as normal. Three months later, ALT increased to 48 U/L, AST 22 U/L (normal values 0-19). Therapy was discontinued and the patient recovered.

WAES 0210ESP00030 described a male on no concomitant medication who 11 months after starting therapy with Propecia experienced transaminases and triglyceride increased: AST 44 (normal <35), ALT 109 (normal <40), triglyceride 216 (normal <160). Clinical serologies were negative for hepatitis. Propecia was discontinued and the patient recovered.

WAES 0405USA01035 described a 35 year-old male with no reported medical history and no allergies on no concomitant medication who experienced right upper quadrant pain and contacted his physician. Laboratory results revealed AST 70, AP 141 (units not specified). Therapy with Propecia was discontinued and the patient recovered.

WAES 0704USA00021 described a 30 year-old male with hyperlipidemia and no allergies on no concomitant medication who 5 months after starting therapy with Propecia developed hepatic function disorder. AST reported as 74 IU/L, ALT 202 IU/L, GGT 171 IU/L (normal values not provided). The patient was asymptomatic. Therapy with Propecia was discontinued and 1 month later the patient was recovering.

Proscar 5 mg

A total of 128 reports of liver function test abnormality were received from 17 countries worldwide: 62 reports from the USA, 16 from Germany, 15 from the UK, 13 from France, 7 from Australia.

Of the 128 reports, 46 concerned patients older than 65 years, 28 concerned patients 18-64 years of age, and age was unknown in 53 reports.

The 128 reports were stratified according to the time to onset of the reported liver function test abnormality in relation to start of Proscar therapy (Table 3). There were:
• 12 reports where liver function test abnormality developed within the first month of therapy with Proscar
• 37 reports where the time to onset of the reported liver function test abnormality developed between 1 month and 1 year after the initiation of therapy with Proscar
• 22 reports where the time to onset of the reported liver function test abnormality was > than 1 year after the initiation of therapy with Proscar, and
• 56 reports where the time to onset of the reported event was "unknown" or not able to be calculated due to missing information.

Table 3: Distribution of the reports for Proscar with regard to TTO and information provided

TTO	Reports with limited information	Reports with confounding factors	Reports with clinical details and without confounders	Total
≤1 month	4	7	1	12
>1 month - ≤ 1 year	13	19	5	37
> 1 year	6	13	3	22

Unknown	47	9	0	56

At least two reports reported positive de-challenge:

WAES 96065530 described a 66 year old male with a history of coronary bypass and concomitant aspirin and nifedipine therapy who had complaints of abdominal pressure, pale stools, dark urine and jaundice 24 days after starting therapy with Proscar. Laboratory analysis revealed ALT 335 U/L (UNR 22 U/L), AST 295 U/L (UNR 18 U/L), GGT 112 U/L (UNR 28 U/L), tBili 4.0 mg/dl (UNR 1 mg/dl) and monocytes 11.6 %. Diagnostic workup revealed no gallstones and hepatitis serologies were negative. Therapy with nifedipine and aspirin continued. Six weeks after therapy with Proscar was discontinued the patient recovered.

WAES 93046069 described a male, age not reported with hypertension on concomitant therapy with alfuzosine, bisoprolol, and aspirin who after 4 months of therapy with Proscar developed "doubtful" sub-icterus. Lab tests revealed AST 89 U/ML, ALT 68 U/ML, normal bilirubin 6 mg/l (normal range not specified). Proscar was discontinued and the patient recovered. Hepatitis (HBS AG, HBS AC, HBC AC) was negative.

In conclusion, the MAH summarised, that the majority of the reports were confounded, describing abnormalities or concomitant therapies that may independently predispose to the development of the reported adverse events and/or contain limited clinical detail precluding adequate assessment. The details of the remaining reports show no consistent pattern in either type of LFT abnormality, clinical presentation, including temporal relationship, or diagnostic findings, that would suggest a single underlying etiology to establish a causal association to therapy with finasteride.

A Merck WAES database analysis of spontaneous reports of LFT abnormality with finasteride corresponded to a PRR of 0.87 (95% CI 0.78-0.97). Another statistical analysis: a disproportionality analysis of the publicly available FDA spontaneous reports comparing the ratio of reporting of ALF with finasteride to ALF with all other drugs was 0.57, indicating that ALF was reported less with finasteride than with all other drugs. Separate analyses for each individual ALF term showed similar magnitude of reporting with finasteride versus all other drugs. Therefore, based on this information, there is no evidence to support a possible signal between therapy with finasteride and liver function test abnormality events.

Based on this post-marketing review of the data as well as numerical/statistical analysis of post-marketing experience and review of clinical trial data, there is no clear evidence that therapy with finasteride is associated with liver function test abnormality.

Assessor's comment:
The safety concern regarding increased hepatic enzymes in relation to treatment with Propecia was identified as early as in the assessment of the second PSUR, and the MAH was requested to monitor closely this safety issue. After the assessment of the third PSUR the MAH was requested to update the SPC with term "hepatic enzymes increased". The MAH refused to update the SPC, and have sent several reviews from that time trying to justify non-inclusion. However, assessments of these reviews led to the same conclusion: the causal associated between finasteride therapy and increased hepatic enzymes cannot be denied and the SPC should be updated.

The most of the reports (152 out of 228) of abnormal hepatic function test contain limited information and cannot be evaluated. Very little information was provided for reports with confounding factors. In the majority of these reports no information on duration and action taken with regard to concomitant treatment was specified, which precludes evaluation of these reports. The MAH could have shown more effort in requesting follow-up information. No other additional pharmacovigilance activities were undertaken by the MAH either.

The MAH has performed disproportionality analysis of the Merck WAES database and FDA database, and concluded that the PRR values for LFT abnormalities with finasteride are below the

threshold value. However, it should not be forgotten that disproportionality analysis in only one of the methods for signal detection, and should not be overestimated.

Additional reports of increased hepatic enzymes were received during the PSUR period 07-Nov-2006 to 06-May-2007. Only the serious cases were discussed by the MAH. Two literature cases published in Farmacia Hospitalaria 2006; 30 (6): 385 were non-serious and were omitted from any discussion. However, these cases are of specific interest:

- One case with a positive re-challenge concerned an 18 year-old male who presented with increased values of GOT and GPT (56 and 78, respectively) after 16 months therapy with finasteride 1 mg for hair loss. Tests for HVB, HVC and immune hepatitis were negative. Three months after discontinuation of finasteride, GOT and GPT return to normal values (26 and 31, respectively). The patient restarted treatment with finasteride voluntary and 2 month later he presented with increased GOT and GPT (49 and 53, respectively) again.

- The second case with a positive de-challenge, concerned a 42 year-old patient who experience increased GOT and GPT (52 and 71, respectively) after 1.5 years treatment with finasteride. Omeprasol was taken concomitantly (for at least 5 years). The patient suspected omeprasol and discontinued it. However, transaminases remained elevated. Then omeprasol was reintroduced and finasteride discontinued, and the values returned to normal.

These cases support the previous conclusion that finasteride may cause an increase in hepatic enzymes. The MAH is requested to include term "hepatic enzymes increased" in section 4.8 of the SPC with frequency "unknown".

Persistence of erectile dysfunction

The MAH has submitted a response to the assessment report on PSUR (7-Nov-2005 – 6-Nov-2007) where summary of pre-clinical, clinical and post-marketing data were presented.

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. 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 supports 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 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 postmarketing 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 MAH 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.

Assessor's comment:
Unfortunately, the MAH has not presented any new data in his response. The MAH is of the opinion that data from clinical trials with finasteride should be considered over that of reports received from the post-marketing environment with regard to determining relationships between drugs and AEs. It is agreed, that clinical trials data are more reliable than post-marketing data. The main advantage of clinical trials is randomisation, existence of a control group and close monitoring. However, this setting includes several disadvantages too: limited number of patients, inclusion of 'ideal patients' (inclusion and exclusion criteria are applied for enrollment), limited duration of treatment. Approximately 1500 patients received finasteride in clinical studies for. In this cohort, only ADR with frequency 1:500 is likely to be detected. The cumulative exposure in post-marketing setting for Propecia is more than 4.5mln patient-year, therefore rare and very rare ADR can be identified. Thus, the importance of post-marketing data should not be underestimated. Many well known examples are supporting this.

The MAH interpretation of post-marketing surveillance (pharmacovigilance) is not in line with the Volume 9A Of the Rules Governing Medicinal Products in European Union. It is not only a tool for signal detection, but it is a system for continuous benefit-risk assessment of the product after marketing authorisation.

One clinical trial report of erectile dysfunction and several post-marketing reports showed that erectile dysfunction had not abated after treatment discontinuation. A typical time to recovery was 2-3

months with a range from 1 day to 4 years. Recently the MPA received one additional case report of persistence of erectile dysfunction:

- The report described a 30 year-old male who have been experienced erectile dysfunction, decreased libido and decreased sperm production for one year after discontinuation of finasteride 1 mg. These AEs appeared together with an increased hair grow.

The MAH is requested to update the SPC with information on possible persistence of erectile dysfunction after discontinuation of treatment with finasteride.

Cardiac disorders

In response to a RMS request, a cumulative review of spontaneous reports of cardiac disorders in patients on therapy with finasteride 1 mg and 0.2 mg tablet was provided.

A total of 96 HCP reports of cardiac disorders were retrieved from the search of the WAES database, 23 serious and 73 non-serious reports. The reports were received from 14 countries worldwide: 45% of reports were received from Japan, 16% from Germany, 18% from the United States and the remaining 21% of the report distribution were among 11 other countries. All reports concerned males with the highest reported age range being patients 30-54 years. Adverse cardiac events are presented in Table 4.

Table 4: Summary tabulation of adverse events in SOC Cardiac disorders

System Organ Class Preferred Term	Total Events*	Serious Events	Non Serious Events
Acute myocardial infarction	1	1	0
Angina pectoris	4	3	1
Arrhythmia	9	0	9
Atrial fibrillation	8	4	4
Atrioventricular block	1	1	0
Atrioventricular block second degree	1	0	1
Bundle branch block right	1	0	1
Cardiac arrest	1	1	0
Cardiac discomfort	3	0	3
Cardiac disorder	1	1	0
Cardiac failure	1	1	0
Cardiomyopathy	1	1	0
Cardiovascular disorder	3	0	3
Cyanosis	1	0	1
Extrasystoles	4	0	4
Hypertrophic cardiomyopathy	1	0	1
Myocardial infarction	6	6	0
Myocarditis	1	1	0
Palpitations	30	2	28
Sinus tachycardia	4	1	3
Supraventricular extrasystoles	1	0	1
Supraventricular tachycardia	2	0	2
Tachycardia	18	2	16
Tachycardia paroxysmal	1	0	1
Ventricular extrasystoles	2	0	2
Ventricular tachycardia	2	1	1
Total Events for Cardiac disorders:	108	26	82
Total number of case reports:	96	23	73

Twenty-three serious reports were received during this cumulative period. Of the 23 reports, 7 reports lacked sufficient details regarding medical history, concomitant medications, or cardiac evaluation which limits meaningful interpretation of these reports.

Eleven reports were identified in which the patients' concurrent conditions and/or concomitant medications may have contributed the reported cardiac disorder event.
Only one report from the remaining five described no other possible causes and was judged by the reporter as possibly related to finasteride:

> WAES 99035618 concerned a 24 year-old a male who experienced tachycardia approximately one month after starting therapy with finasteride (0.5 mg twice daily). No organic reason for the arrhythmia were identified, no obvious psychic component was present. Therapy with finasteride was continued and atenolol was initiated. The patient recovered and two days after hospital discharge the patient developed sinus tachycardia which still persisted at the time of the report. His finasteride dosage was reduced to 0.5 mg daily.

There were 73 non-serious reports received. The most frequent non-serious cardiac events included palpitations (28), tachycardia (16) and arrhythmia (9). Sixty-one (61) of the 73 reports lacked sufficient details regarding medical history, concomitant medications, or cardiac evaluation which limits meaningful interpretation of these reports. Eight (8) reports were identified in which the patients' concurrent conditions and/or concomitant medications may have contributed the reported cardiac disorder event.

The following reports described positive re-challenges:

> WAES 00010552 describes a 41 year-old male who experienced headache, palpitations and swelling of the head after approximately 2 weeks of finasteride therapy. Therapy was discontinued and his symptoms abated. His symptoms recurred upon re-starting finasteride.
>
> WAES 98031581 describes a 35 year-old male who experienced heart palpitations, rapid heartbeat, headache, a funny taste in his mouth, lightheadedness, general confusion and an uneasy feeling that he described as "being afraid to talk to co-workers due to feeling like what he said may not make sense" after approximately 1 day of therapy with finasteride. These events reported abated upon interruption of therapy and recurred after restarting finasteride.
>
> WAES 00069353 describes a 28 year-old male physician, who after approximately 4 months of therapy with finasteride, experienced palpitations with increasing frequency over the course of three weeks. The patient was evaluated by a cardiologist, ECG showed sinus tachycardia and sinus arrhythmias, thyroid tests normal. On the fourth week the patient reported dizziness and blurred vision before the palpitations. Finasteride was discontinued and reportedly his symptoms disappeared 48 hours after suspension of the therapy. Five days after suspension of the therapy, the consumer decided to restart the treatment with finasteride but symptoms re-appeared in the next 48 hours, so therapy was discontinued. Subsequently, the patient recovered from palpitations.

As of 18-Aug-2007 Merck has received from HCPs 96 reports of cardiac disorders involving patients who were being treated with finasteride 0.2 mg, and 1 mg. In the majority of the reports where the patient was not reported to have an underlying condition and/or concomitant medication that could have caused cardiac disorders, there is insufficient data to evaluate the relationship with cardiac disorders. Many of the reports were confounded, describing abnormalities or concomitant therapies that may independently predispose to the development of the reported adverse events including history of congenital heart disease, irregular heart rate, atrial fibrillation, myocardial infarction, hypertension, hypercholesterolemia, angina, alcohol use, cocaine use and smoking. In summary, review of reports of cardiac disorder in patients receiving finasteride during the period of this review does not suggest that treatment with finasteride predisposes the patient to the development of cardiac disorders.

Assessor's comment:
In total there were 30 reports of palpitation and 18 reports of tachycardia identified. Few reports reported a clear positive re-challenge which confirms a causal relation with finasteride. A vast

majority of reports with confounding factors were not presented and cannot be evaluated. However, based on the data presented it seems reasonable to include palpitation in to the SPC.

Psychiatric disorders

Comment on Rahimi-Ardabili article regarding Finasteride and Depression
The authors conducted a study of men with androgenetic alopecia who were prescribed finasteride 1mg/day (n=144). Information on depressed mood and anxiety were obtained prospectively using the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS) prior to treatment and after two months of treatment. Results presented included data on 128 of the 144 enrolled men; data on the 16 enrolled men who did not complete the study are omitted. Based on data from the 128 men who completed the study, the authors report a significant change ($p<0.001$) in the BDI score over the study period (pre treatment score [mean±SD] 12.11 ± 7.50; post-treatment score 12.80 ± 7.64) and a significant change ($p=0.005$) in the HADS depression score (HADS-D) (pre-treatment score 4.04 ± 2.52; post-treatment score 4.61 ± 3.19). Change in HADS anxiety score (HADS-A) increased nonsignificantly (pre-treatment score 6.24 ± 3.17; post-treatment score 6.60 ± 3.06).

The authors do not provide interpretation of the clinical relevance of the observed changes in the BDI or HADS-D instruments. Of note, no adverse experiences of depression were reported, consistent with the small mean changes observed and supporting that the changes in the BDI and HADS-D scores are unlikely to be clinically meaningful. Conversely, nearly 10% of patients reported sexual dysfunction over the 2-month period of the study. This event rate is higher than that seen in other clinical trials, making it unlikely that the lack of adverse experience reports of depression was due to a non-reporting bias on the part of the patients enrolled in this study.

There are several limitations of this study. First, it is unclear how patients were selected for the study, since randomization was not used in part because the study lacked any control group(s). More than half of the population of men enrolled had, in fact, evidence of depression at baseline based on one of the instruments used, the BDI, to assess the study outcome. Second, the study design did not utilize treatment blinding; patients and investigators were aware that each participant received the study drug. Third, the high rate of reports of sexual dysfunction might lead to an increase in depression score and confound interpretation of the study outcome. The authors apparently realized the limitations of their study design and attempted to mitigate them. For example, they advised patients that the effect of finasteride on hair growth might not be apparent during the 2-month duration of the study, so as to minimize any confounding depression that might arise due to failure of the drug to meet patient expectation of treatment response. The authors were also concerned that, given the uncontrolled, open label, unblended design of the study, that the small changes in depression scores observed might be secondary to effects of finasteride on sexual function. The authors assessed this possibility through statistical assessment among those patients reporting sexual dysfunction and the degree of change in psychometric scores. While no significant association was detected, the absence of a control group makes interpretation of this potential confounding effect difficult.

The most likely interpretation of the results of this study is that they represent natural fluctuations over time in a group of young men, the majority (53%) of whom had objective evidence of depression at baseline. In support of this conclusion, as part of the development program for finasteride 1 mg, the Sponsor conducted three, 1-year, double-blind, placebo-controlled Phase III clinical trials of finasteride 1 mg in men (ages 18 to 41 years) with androgenetic alopecia (P087, P089 and P092). In a pooled analysis of these 3 studies (N=1879), depression was reported by 6/945 (0.6%) of men randomized to finasteride 1 mg and 8/934 (0.9%) of men randomized to placebo. The Sponsor also conducted two 2-year, double-blind, placebo-controlled studies, one in the same age range as the Phase III studies in men with advanced hair loss (P114) and one in older men (ages 41 to 60 years) with androgenetic alopecia (P121). In P114, depression was reported by 3/272 (1.1%) of men randomized to finasteride and 3/139

(2.2%) of men randomized to placebo. In P121, depression was reported by 5/286 (1.7%) of men randomized to finasteride and 1/138 (0.7%) of men randomized to placebo.

The published papers referenced by the authors (Rahimi-Ardabili et al 2006) contradict available data from detailed studies done in support of registration of finasteride and there is no data in support of their hypothesis that inhibition of DHT results in depression. Furthermore, most of the data from studies conducted at Merck were published in peer reviewed journals (Clark et al 1990; Wise et al 1991). Finasteride has been extensively evaluated for safety and efficacy in laboratory animals. The studies included detailed developmental toxicity studies in rats where postnatal behaviors were evaluated following finasteride exposure during prenatal and perinatal period. In addition, detailed studies in male rats given high doses of finasteride chronically, demonstrated there was no evidence of depression behavior as described in one of the referenced papers by the authors.
Taken together, these data do not suggest that the use of finasteride 1 mg is associated with depression in men with androgenetic alopecia.

Assessor's comment:
The MAH was asked to comment on a study published by Rahimi-Ardabili B et al. and discuss a possible mechanism described by the authors. Unfortunately, in depth analysis is missing and only some generalised critical comments provided. Psychiatric disorders should continue to be monitored.

Other issues of possible interest

Assessor's comment:
No discussion was provided on cases with other unlisted adverse events. The following cases of possible interest should be discussed by the MAH: infertility (7), infertility male (8); nipple disorder, nipple pain, nipple swelling (1; 13; 3); haematospermia (22), semen discolouration (16); erythema (annulare, multiforme, nodosum, generalised); malaise (44), dizziness (37), headache (37), somnolence (22), hypoaesthesia (12), paraesthesia (13); abdominal pain (34), diarrhoea (30); flushing, hot flushes (6; 12). Both serious and non-serious cases should be included into analysis and evaluated with regard to indication, duration of treatment, TTO, concurrent diseases, concomitant therapies, outcome and action taken with finasteride and concomitant therapy. Possible additive role of finasteride should be assessed in cases with confounding factors. CIOMS forms of these cases should be also provided.

9.2 Drug interactions

No new safety issue has been identified.

9.3 Overdose and its treatment

No new safety issue was identified.

9.4 Abuse or misuse

No new safety issue was identified.

9.5 Medication errors

From market introduction until the 06-05-2007, there were 256 reports identified from HCP. Of the 256 reports of medication error with Propecia, 63 reports (25%) contained serious ADRs. Of these 63 reports with serious ADRs, 18 reports did not contain any other serious ADR other than the reported medication error term. Of the total 63 reports with serious ADRs, 29 involve exposure to Propecia

during pregnancy (discussed in section Pregnancy and lactation). Of the remaining 34 reports, 13 reports involved exposure of Propecia to children and 5 reports involved female exposure. The remaining 16 reports involved medication error in male patients.

Of the 13 reports of exposure of children, all but one described accidental exposure and none of them described any adverse event.

Of the 5 reports of female exposure, in one report the patient had no direct dermal or ingestion of finasteride. In the remaining four reports the following AEs were reported: uterine disorder and vaginal haemorrhage; breast cancer; cerebrovascular accident; ovarian cyst. The majority of the reports were insufficient for evaluation, information regarding action taken with Propecia therapy, dose and duration of therapy, concomitant medications and/or concurrent conditions/medical history was not provided. A few reports described concurrent conditions/medical history and/or concomitant therapy which may have contributed to the reported events. There is no pattern among the reported events that would suggest a causal association to therapy with Propecia or specifically related to misuse or medication error with the product.

The remaining 16 serious reports involve males with medication error. In these 16 reports, 6 reports involved splitting or crushing Propecia tablets, 5 reports described an inappropriate schedule of drug administration and the remaining 5 reports described other medication errors with Propecia.

No new safety issues relating to medication error were identified during the ongoing monitoring of the safety of Propecia. The Company will continue to monitor reports of medication error with Propecia.

Assessor's comment:
Quite a number of cases of medication error were reported to the company. A summary tabulation of all AEs related to medication error was provided. The serious cases were discussed. No specific ADR was identified from these reports. However, a high number of reports on medication error remains a concern and should be further monitored.

9.6 Death

No case with fatal outcome was identified during the PSUR and addendum period (07-11-2006 – 18-Au-2007). No information on this topic was provided in the summary bridging report.

9.7 Pregnancy and Lactation

A cumulative review (from 11-Sep-1997 to 06-May-2007) of pregnancy outcomes for Propecia was provided. A total of 327 spontaneous (HCP and consumer) and study reports of potential exposure to Propecia during pregnancy and lactation were received. Routes of exposure include semen, dermal, oral and inhalation.

Of the 327 total potential exposure to Propecia during pregnancy reports received, 152 reports had no outcome provided with respect to the reported pregnancy and are not further discussed.
Of the remaining 179 reports, 82 reports were received from HCPs including regulatory agencies, 38 reports from consumers, 55 reports from the study environment and 4 reports of exposure during lactation/breast feeding. Table 5 presents pregnancy outcomes with regard to report type.

Table 5: Pregnancy outcomes

Pregnancy outcome	HCP reports			Consumer reports			Study reports
	Semen	Derma	Oral	Semen	Derma	Oral	Semen

			1						1					
	R	P	R	P	R	P	R	P	R	P	R	P	R	P
Ectopic pregnancy														
Elective termination, no foetal defects	2	1		2		2	1	3				1	1	3
Elective termination with foetal defects	3												1	
Spontaneous abortion	21	1					11				1		4	2
Stillbirth without foetal defects	1		1					1					1	
Stillbirth with foetal defects	1													
Live birth without congenital anomalies	5	25		2		4	3	3		1			19	21
Live birth with congenital anomalies	11	1					5						1	1

A majority of the reported finasteride exposures described potential transmission via semen with the remaining reports describing exposure via dermal/inhalation contact (mostly from pharmacists), maternal ingestion when prescribed for unapproved indication and exposure during breast feeding.

The conclusion of these analyses is that exposure of pregnant women to semen of men taking finasteride does not constitute a risk to the developing male foetus. As indicated in the prescribing information for Propecia, administration of finasteride to women is contraindicated and there are clear statements concerning the potential risk of dermal exposure to the drug. Merck continues to monitor reports of potential exposure of pregnant women to finasteride. The current prescribing information for Propecia adequately describes the risks associated with use of finasteride or handling of broken tablets by women who are or may be pregnant. The Company will continue to monitor reports of exposure to Propecia during pregnancy/lactation.

Assessor's comment:
This safety issue has been thoroughly reviewed in several PSURs, last time in the PSUR for the period 07-11-2005 – 06-11-2006. The data in the Table 5 shows that the majority of cases with spontaneous abortion or congenital anomalies were reported retrospectively. These cases may include reporting bias and should be evaluated carefully. It is agreed that no new safety issue were identified from these reports and no update to the SPC regarding drug use in pregnancy is warranted at the moment. However, drug use in pregnancy should remain under close monitoring.

9.8 Special Patients Groups

Paediatric patients
Cumulative reviews of reports in paediatric patients and specifically in adolescents were provided.

From 11-09-1997 to 06-05-2007 a total of 55 reports were received in this patient group (18 years and younger). The most commonly reported AEs were from the following SOCs: Injury, poisoning and procedural complications (23), General disorders and administration site conditions (21), Reproductive system and breast disorders (12), Skin and subcutaneous tissue disorders (5).

From market introduction (11-Sep-1997) to 18-Aug-2007 a total of 31 spontaneous reports were identified in adolescents. Five of the 31 spontaneous reports identified met the regulatory criteria for a serious report; the remaining 26 reports were non-serious. Seventeen reports were received from healthcare providers (HCPs) including regulatory agencies and 14 reports were received from consumers. All reports were male. Information on patient age included 28/31 (90%) patients between 15 to17 years of age and the remaining 3 patients were 13 (1 report) and 14 (2 reports) years old. The majority of reports were received from the United States. Indications for treatment with finasteride therapy reported in these reports in order of decreasing frequency included alopecia, hair loss and male pattern baldness.

The majority of AE reports involving use of finasteride in adolescents reflect the AE profile seen in patients with regular use of finasteride. The SOCs with the 3 highest numbers of reports included:

Reproductive system and breast disorders (N= 10), Skin and subcutaneous tissue disorders (N= 8), General disorders and administrative site conditions (N=5) and Injury, poisoning and procedural complications (N=5). Reports related to hair growth or loss were captured in the SOC Skin and subcutaneous tissue disorders. The reproductive system and breast disorders SOC reflected reports of male reproductive and/or breast related adverse events. General disorders and administrative site conditions included the terms "no adverse effect and drug ineffective". Injury, poisoning and procedural complications SOC captured the event "drug administration error" making up the majority of the reports. A review of these individual reports did not reveal any new safety signals.

Female patients

In response to the request from the Swedish Medical Products Agency (MPA) a cumulative review of world-wide data of off-label use of finasteride 0.2 mg and 1 mg tablets in women was provided.

A total of 206 spontaneous reports were identified from this search. Fourteen of the 206 spontaneous reports identified met the regulatory criteria for a serious report; the remaining 192 reports were non-serious. Seventy-two reports were received from healthcare providers (HCPs) including regulatory agencies and 134 reports were received from consumers. Information on patient age was provided in all reports. One hundred and fifty-two of 206 patients (74%) patients were between 18 to 64 years of age and 54/206 (26%) patients were ε65 years of age. The highest majority of the patients fell into the age group 50 to 54 years: 32/206 (16%). Reporting rates of adverse events remained consistently low over time and the majority of reports were received from the United States. Indications for treatment with finasteride therapy in order of decreasing frequency included hair loss, alopecia, hair thinning, female pattern baldness, hirsutism, baldness, hormonal imbalance, polycystic ovaries, testosterone high, hair growth abnormal and scalp pain.

The SOCs with the 4 highest numbers of reports included: Injury, poisoning and procedural complications (N=144), Skin and subcutaneous tissue disorders (N= 57), General disorders and administrative site conditions (N=50) and Reproductive system and breast disorders (N= 22). Review of the data by SOC revealed that the Injury, poisoning and procedural complications SOC captured the event "drug administration error" making up the majority of the reports. Reports related to hair growth or loss were captured in the SOC Skin and subcutaneous tissue disorders. General disorders and administrative site conditions included the terms "no adverse effect and drug ineffective". The reproductive system and breast disorders SOC reflected reports of gynecological and/or breast related adverse events, which would be anticipated in a female population. A review of these individual reports did not reveal any new safety signals.

In the recent Assessment Report for the Propecia PSUR (07 Nov 05 to 06 Nov06), MSD was requested to "suggest risk minimization activities as the drug is prescribed off label for women and adolescents".

Following a discussion with the MPA in June 2007, the Company agreed to include a cross reference from section 4.3 of the EU SPC to section 5.1 which includes results from a study in postmenopausal women with androgenic alopecia who were treated with finasteride 1 mg for 12 months and in which no efficacy compared to placebo was observed. In addition, the Company agreed to consider strengthening the warning for use in children in section 4.4, warnings and precautions to indicate that this warning is based on lack of efficacy and safety data in children and adolescents under the age of 18. These proposed EU SPC label changes are listed below (in **bold**).

Section 4.3

Contra-indicated in women: see 4.6 Pregnancy and lactation **and 5.1 Pharmacodynamic properties.**
Hypersensitivity to finasteride or to any of the excipients.

Section 4.4

PROPECIA should not be used in children. **There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.**

The Company will continue to monitor reports of off-label use in women and adolescents.

Assessor's comment: Proposed changes to the SPC are endorsed. Off label use in women and paediatric patients should continue to be monitored.

9.9 Long-term treatment
No new information was provided.

10. Difference Reference Safety Information – CCSI vs SPC
There are no meaningful differences.

11 Conclusion in PSUR by the MAH
Analysis of these data contained within this Summary Bridging Report supports the adequacy of the current CCDS for finasteride, 1 and 0.2 mg, MSD in terms of product safety.

Examination of the data contained within this Summary Bridging Report supports the conclusion that the overall benefit-risk balance for finasteride, 1 and 0.2 mg, MSD continues to be positive.

As with all Merck & Co., Inc. products, the safety profile of finasteride, 1 and 0.2 mg, MSD is closely monitored on a continuing basis.

11. Comments on report
The quality of the report is acceptable.

12. Comments on SPC/PIL/Labelling

SPC
Section 2
Lactose monohydrate should be included here as an excipient. Also, since some of the excipients contain sodium, there should be a statement in this section according to the Guideline on "Excipients in the label and package leaflet of medicinal products for human use": "This medicinal product contains less than 1 mmol of sodium per tablet".

Please correct to the standard sentence "For a full list of excipients, see section 6.1."

Section 4.8
Section 4.8 should be revised according to the Guideline on Summary Product characteristics.

The first sentence "Undesirable effects have usually been transient during treatment or resolved upon discontinuation" should be deleted.

ADR should be listed in one table. The names of SOC and frequencies of ADR should be revised according to Guideline. No frequencies should be used for ADR identified in post-marketing setting. They should be listed under frequency "not known".

The terms "increased hepatic enzymes" and "palpitation" should be included into section 4.8.

Additionally, information on duration/persistence of some ADR (e.g. erectile dysfunction, breast disorders, and libido) should be included either to section 4.4 or section 4.8.

Section 6.1:
The origin of pregelatinized starch (e g maize) should be stated.
The excipient "hyprolose" should be changed to "hydroxypropylcellulose".
"Yellow and red ferric oxide" should be changed to "yellow and red iron oxide".

PIL and labelling text

The applicant has proposed a harmonised PIL and labelling text. **The labelling text is considered acceptable, but RMS has a few comments on the proposed PIL:**

In section 2 "Do not take XXX"revisions should be made as shown in the enclosed PIL (highlighted changes). It is superfluous to repeat that the product should not be taken under these circumstances. And the sentence "If you are not sure..." should be part of the second bullet (since we hope that patients are sure whether they are female or not).

In section 5 a few corrections must be made as shown in the enclosed PIL. "EX" is not an accepted abbreviation for expiry date on the cartons. Also, it is not acceptable to print the expiry date as MM/YY. The year must be stated with 4 digits on the packages.

User test

The package leaflet has been user tested via the LUTO user testing process. After a pilot testing, the PIL was revised and thereafter tested in 20 participants. After further revision, the PIL was retested in another 21 subjects.

All participants were men, which is considered accurate in this case. The participants were of varying age and educational level.
The questions covered the main parts of the PIL.

The results of the user test demonstrates that at least 90% of the participants were able to find each point of information and express it in his/her own words.

RMS considers the user test acceptable.

14. GMP

No GMP issues remains.

15. Quality

The Marketing Authorisation Holder has confirmed that the quality of the finished products with respect to the methods of preparation and control, has been updated regularly by variations to take account of technical and scientific progress in accordance with article 23 of directive 2001/83/EC as amended by Directive 2004/27/EC and that the product conforms with current CHMP quality guidelines.
The composition of the finished product, and the currently approved specifications for the drug substance and the drug product have been provided.

Assessor's comments on the composition of the drug product:
For the following excipients the applicant gives solely NF or USP as quality reference: Pregelatinized starch, sodium starch glycolate and docusate sodium. All these three excipients have monographs in the Ph. Eur. The applicant is requested to update the composition of the finished product to include the Ph. Eur. quality reference for the excipients.

Assessor's comments on the drug substance specification (finasteride):

There is a monograph in the Ph. Eur. for finasteride. The applicant is requested to provide an updated specification for the drug substance, from which it should be evident that the drug substance used in the manufacture of Propecia and Capipro complies with the Ph. Eur. monograph. Also, the specification for individual unknown impurities should comply with the Ph. Eur. monograph for Substances for pharmaceutical use, i.e. NMT 0.10%.

16. Conclusion and recommendation by the assessor

Based on the data provided and the current knowledge it may be concluded that information about benefit and risk of Propecia is not adequately assessed and communicated to the healthcare professionals and consumers by the MAH. This may negatively affect rights, safety and well-being of patients.

Benefit-risk assessment will be made after the response of the MAH to the following issues:

1. *Discussion on the following safety issues should be provided: infertility (7), infertility male (8); nipple disorder, nipple pain, nipple swelling (1; 13; 3); haematospermia (22), semen discolouration (16); erythema (annulare, multiforme, nodosum, generalised); malaise (44), dizziness (37), headache (37), somnolence (22), hypoesthesia (12), paresthesia (13); abdominal pain (34), diarrhoea (30); flushing, hot flushes (6; 12). Both serious and non-serious cases should be included into analysis and evaluated with regard to indication, duration of treatment, TTO, concurrent diseases, concomitant therapies, outcome and action taken with finasteride and concomitant therapy. Possible additive role of finasteride should be assessed in cases with confounding factors. CIOMS forms of these cases should be also provided. The SPC should be updated accordingly, if appropriate.*

2. *The consideration of the MAH to include only reports where Propecia was primary suspected drug does not comply with the Volume 9A. The MAH should present a total number of cases were Propecia was suspected therapy. Line listing of not included cases should be also provided.*

3. *Revision of product information (SPC and PIL)*

   <u>The following amendments to the SPC should be made:</u>

   Section 2

   Lactose monohydrate should be included here as an excipient. Also, since some of the excipients contain sodium, there should be a statement in this section according to the Guideline on "Excipients in the label and package leaflet of medicinal products for human use": "This medicinal product contains less than 1 mmol of sodium per tablet".

   Please correct to the standard sentence "For a full list of excipients, see section 6.1."

   Section 4.8

   Section 4.8 should be revised according to the Guideline on Summary Product characteristics.

   The first sentence "Undesirable effects have usually been transient during treatment or resolved upon discontinuation" should be deleted.

ADR should be listed in one table. The names of SOC and frequencies of ADR should be revised according to Guideline. No frequencies should be used for ADR identified in post-marketing setting. They should be listed under frequency "not known".

The terms "increased hepatic enzymes" and "palpitation" should be included into section 4.8.

Additionally, information on duration/persistence of some ADR (e.g. erectile dysfunction, breast disorders, and libido) should be included either in section 4.4 or section 4.8.

***Section 6.1**:*
The origin of pregelatinized starch (e g maize) should be stated.
The excipient "hyprolose" should be changed to "hydroxypropylcellulose".
"Yellow and red ferric oxide" should be changed to "yellow and red iron oxide".

The following amendments to the PIL should be made:
Please see enclosed PIL with highlighted changes.

4. *The applicant is requested to update the composition of the finished product to include the Ph. Eur. quality reference for the excipients.*

5. *The applicant is requested to provide an updated specification for the drug substance, from which it should be evident that the drug substance used in the manufacture of Propecia and Capipro complies with the Ph. Eur. monograph. Also, the specification for individual unknown impurities should comply with the Ph. Eur. monograph for Substances for pharmaceutical use, i.e. NMT 0.10%.*

The changes to section 4.3 and 4.4 of the SPC proposes by the MAH are endorsed.

At the moment renewal of the marketing authorisation cannot be recommended.