LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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Propecia/Capipro

SE/H/158/001

Final Assessment Report of PSUR

Active substance	***Finasteride***
Administration form	Film-coated tablets
MAH	Merck Sharp & Dohme
International birth date/ European birth date	**11 September 1997 (Mexico)**
Period of PSUR	7 November 2005 – 6 November 2006
RMS's Preliminary AR	15 March 2007
Comments by CMS	4 April 2007
Final AR	18 April 2007
Clinical assessor	Jolanta Gulbinovic, MD
Project manager / Contact person	Ms. Anna Litzén
Responsibility of decision	Gunilla Sjölin-Forsberg, MD, PhD

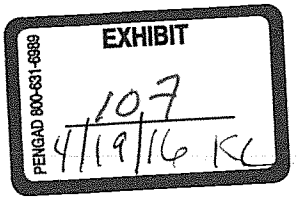
1 Introduction

Finasteride, an active substance of Propecia, is a synthetic 4-azasteroid compound that is specific inhibitor of type II 5α-reductase, an intracellular enzyme that metabolizes the androgen testosterone into dihydrotestosterone (DHT). In men with male pattern baldness, the balding scalp contains miniaturized hair follicles and increased amounts of DHT. Finasteride inhibits the process leading to miniaturization of the scalp hair follicles, thus counteracting male hair loss.
Finasteride, 1 mg, is indicated for the treatment of men with male pattern hair loss (androgenic alopecia) to increase hair growth and prevent further hair loss.

Two 6-months PSURs and Summary Bridging Report for Propecia (1 mg and 0.2 mg), covering period 07 November 2005 – 06 November 2006 were submitted.

In the previous 1-year PSUR AR it was concluded:

- *Submitted data revealed new safety information requiring the following amendments to the SPC:*
  - *Abnormal liver function tests should be included in section 4.8 of the SPC.*
    The Type II variation should be submitted within two months.
- *Moreover, in the next PSUR the MAH should present the cumulative reviews of all cases of testicular cancer, psychiatric disorders, outcome of pregnancies after exposure to finasteride during pregnancy, and of all cases of misuse and off-label use.*
- *The MAH should further monitor hepatobiliary disorders, psychiatric disorders, neoplasms and outcome of pregnancies after exposure to finasteride during pregnancy.*
- *The MAH should show more compliance with the Volume 9 of The Rules Governing Medicinal Products in the EU and OCH guideline E2E.*



Assessor's comment: The MAH did not agree to update the SPC with term Hepatobiliary disorders, instead a new cumulative review on this topic has been submitted. An assessment is presented in section 8.1.2.

2 Worldwide Marketing Authorisation Status

Finasteride 1 mg was first approved in Mexico on 11-09-1997, and is currently approved in 62 countries. Finasteride 0.2 mg was first approved in Japan on 05-10-2005, and is currently approved in 1 country. There are no records of any registration being revoked or withdrawn for safety reasons.

Assessor's comment: The MAH should provide explanation for different finasteride doses used for the same indication in Japan and other countries.

3 Regulatory authority or MAH action for safety reasons

None related to finasteride, 1 mg and 0.2 mg, during the reporting period.

4 Changes to Reference Safety Information

During the reporting period there were no safety related changes to the CCDS for finasteride, 1 mg and 0.2 mg.

5 Patient exposure / Quantities dispensed worldwide

Clinical trials

There were no patients enrolled in Merck-sponsored clinical trials and treated with finasteride, 1 mg and 0.2 mg.

Market experience

The numbers of patients treated with Propecia (finasteride, 1 mg and 0.2 mg tablets) are presented in the Table 1 below.

Table 1 Patient exposure: Market experience

	Period (01-11-2005 to 31-10-2006)		Cumulative (market launch to 31-10-2006)	
	Tablets	Patient years	Tablets	Patient years
Finasteride 1 mg	222,769,509	610,327	1,534,066,793	4,202,923
Finasteride 0.2 mg	1,638,980	4,490	1,638,980	4,490
Total	224,408,489	614,818	1,535,705,773	4,207,413

Assessor's comment: Patients exposure has increased during this reporting period (539,991 PY during the previous PSUR period). The MAH did not describe how patient exposure was calculated. Apparently, the calculation was based on assumption that every patient has taken one tablet daily (either 1 mg or 0.2 mg). In this case the daily dose for different formulations (e.g. 1 mg and 0.2 mg) differs five times, therefore the MAH should continue to present patient exposure for finasteride 1 mg and finasteride 0.2 mg separately.

6 Presentation of Individual Case Histories / Adverse Events

During the period under review, a total of 597 case reports were received. The increase in the number of spontaneous reports received this reporting period as compared to the prior reporting period (300) can be explained by the increase in the number of spontaneous reports received from Japan (463 reports), where Propecia was launched in January 2006.

Assessor's comment: This section of the PSUR includes only description of the system and the list of appendices (line listings, summary tabulations, etc). No case histories were presented or discussed in this section. From the data presented it is unclear how many ADRs were reported (including serious

unlisted, serious listed, non-serious unlisted and non-serious listed). Although In the previous PSUR assessment report the MAH was asked to show more compliance with the Volume 9, no changes with regard to issues mentioned above were made. The MAH should also check coding terms. The terms "adverse event" (n=4), "no adverse drug effect" (n=9) without any explanation or reference is not acceptable (see PSUR, App. 4. Summary tabulation for spontaneous unlisted reports, p.4). It should also be noticed that adverse drug reactions not case reports are classified as serious unlisted, serious listed, etc. Cumulative number of adverse reactions of interest (e.g serious unlisted) should be always presented. The MAH should also present separate summary tabulations by SOC for finasteride 1 mg and finasteride 0.2 mg, too.

7 Studies

During the reporting period, there were no newly analyzed studies, targeted new safety studies, or published studies that contain important, new safety information for finasteride.

8 Overall Safety Evaluation

8.1 *Serious unlisted ADRs*

During this PSUR period, a total of 62 reports were received from HCP that contained serious unlisted ADRs. The short summary of all reports was provided. The MAH has concluded that no new safety concerns were identified.

Assessor's comment: It is difficult to evaluate the provided reports because the majority of them contained limited information. Fifty (50) case reports were received from the USA, 4 from Germany and the rest of them from the six other countries. It was not specified which ADRs were serious and unlisted in the cases presented. The cumulative number of these ADRs was not provided either. In the future PSURs it should be clearly specified which ADRs are serious unlisted; cumulative number of these reactions should be presented. According to recommendations in the Volume 9, individual case histories should be presented and discussed in section 6 of PSUR.

8.2 *Topics of interest*

8.2.1 Reversibility of adverse reactions related to the male reproductive system

The following reviews were performed after request from the RMS.

Testicular pain

A review of clinical trials data, product labeling and spontaneous reports was provided.

In clinical studies of finasteride 1 mg vs. placebo, the incidence of testicular pain was not different between treatment groups.

A total of 186 reports were received: testicular pain, n=181; testis discomfort, n=8; and scrotal pain, n=5. The majority of these reports (93%) were non-serious, and patients' age ranged from 17 to 75 years. The outcome is provided in table 2.

Table 2 Action taken and outcome of the reported adverse experience

	Total	Therapy discontinued	Therapy continued	Unknown
Recovered/recovering	97	75	16	6
Not recovered	28	9	10	9
Unknown	58	-	-	-

In 28 reports, the ADR persisted at the time of reporting. In two reports, where therapy was discontinued, testicular pain continued for months following discontinuation of finasteride therapy. The MAH considers the current labelling as presented in the side effects section of the CCDS and the undesirable section of the SPC to be appropriate. The company will continue to monitor reports of persistent testicular pain following discontinuation of finasteride therapy.

Assessor's comment: Testicular pain is labelled in the current SPC. The MAH should continue to monitor this safety issue especially with regard to reversibility of symptoms.

Male reproductive system symptoms

A review of clinical trials data, product labeling and spontaneous reports was provided.

Clinical studies

Phase III pivotal studies (087 and 089) with extension phases provided placebo-controlled efficacy and safety data through 5 years of treatment. Three types of adverse experiences were identified during these trials: decreased libido, ejaculation disorder and erectile dysfunction. During a 5-year period, only one patient out of 72 who experienced sexual adverse event reported that the ADR was still present 6 months after discontinuing finasteride therapy. No further follow up information was available on this patient.

Background incidence

The background data on incidence of erectile dysfunction (ED) in some countries were provided. It ranges from 10% to 34% and increases with age, and in association with diabetes, heart disease, lower urinary tract infections, heavy smoking, and depression.

Product labeling

According to the MAH, male reproductive system disorders are well described in the side effect sections of the CCDS: "...the following drug-related adverse experiences were reported in ≥1% of men treated with Propecia: decreased libido (Propecia, 1.8% vs. placebo, 1.3%), and erectile dysfunction (1.3% vs. 0.7%). In addition, decreased volume of ejaculate was reported in 0.8% of men treated with Propecia and 0.4% of men treated with placebo. Resolution of these side effects occurred in men who discontinued therapy with Propecia and in many who continued therapy..."

Post-marketing experience

In the company's safety data base, a total of 617 reports were identified mapping to the following MedDRA PT: erectile dysfunction (392), libido decreased (283), sexual dysfunction (86), loss of libido (18), ejaculation failure (9), ejaculation delayed (7), male sexual dysfunction (1), and organic erectile dysfunction (1). The majority of these reports (93%) were non-serious. Patients ranged in age from 17-78 years. Five reports were excluded from the analysis (in one report, a patient obtained therapy from the internet, and in four reports ADR occurred after therapy with finasteride was discontinued). The outcomes in other reports are provided in table 3.

Table 3 Action taken and outcome of the reported adverse experience

	Total	Therapy discontinued	Therapy continued	Unknown
Recovered/recovering	197	154	32	11
Not recovered	200	100	37	63
Unknown	215	-	-	-

Of the 397 reports where an outcome was provided, half (n=197) described an outcome of recovered/recovering. In 32 of these reports the patients continued on therapy with finasteride and

recovered. Three of these reports described concurrent conditions: diabetes, anxiety, bi-polar disorder. In 154 reports, the patients discontinued therapy and recovered. Twenty two of them had concurrent condition that may influence erectile function. Of the remaining 132 reports only 59 described time to recovery which ranged from 1 day to 4 years with a typical time to recovery of 2-3 months.

In the 200 reports which described the outcome as not recovered, 63 were insufficient for further evaluation. In 37 reports the patients continued on therapy with finasteride at the time of the report. Six of them reported risk factors that may have contributed to the ADR. The remaining 100 reports describe patients whose adverse experience was reported to have persisted upon discontinuation of therapy with finasteride at the time of report. Twenty five (25) of these reports described concurrent conditions that may have contributed to the ADR. The majority of the remaining 75 reports lack sufficient information for further evaluation. In the 22 reports, where some information regarding time duration of the events was provided, there was no pattern as to the nature and degree of the adverse experience, time to onset of the event, and/or length of time the event had persisted following discontinuation of therapy. The time to onset was from 1 week to 4 years and the length of time the ADR has persisted following discontinuation of therapy ranged from weeks to years. Only two of the 72 reports described an endocrine and/or urology work up.

The report WAES 0602USA01491 concerned a 22 year-old male who used finasteride for early male pattern balding. Three to four months later the patient began to experience complete loss of sexual drive, including loss of spontaneous erection. The patient was evaluated by urologist (serum testosterone was within normal limits, 567; testicular ultrasound showed calcifications). Finasteride was discontinued. Eight months later the patients experienced the same symptoms without any signs of spontaneous resolution. Additional diagnostic test were done: complete endocrine lab tests, MRI, serial measurements of testosterone, which have been unremarkable.

The second report WAES 05001GBR00133 concerned a 19 year-old male, who was placed on finasteride 1 mg for male pattern baldness. Subsequently the patient experienced erectile dysfunction, gynaecomastia, fatigue and feeling "mentally unclear". Finasteride was discontinued. The patient's experiences persisted for almost two years, laboratory test results were normal.

The MAH considers that male reproductive system symptoms such as erectile dysfunction and decreased libido are very common with reported incidence rates of 25 per 1,000 man years and are well described in the CCDS. The company will continue to monitor reports of persistent male reproductive system disorders following discontinuation of finasteride therapy.

Assessor's comment: During this PSUR period, it has came to the knowledge of the RMS that information of remaining problems from the male reproductive system after cessation of therapy with Propecia is spread over internet sites. Based on this information an after control protocol (Dnr: 2154:2006/72930) "Regarding reversibility of adverse reactions related to the male reproductive system" was sent to the MAH.
The MAH has provided some data from clinical trials and analysis of spontaneous reports. The data from clinical trials are difficult to interpret with regard to reversibility of male sexual dysfunctions, because the number of subjects included to the studies 087 and 089, patient exposure to finasteride and duration of treatment and follow up were not provided.
Cumulatively 617 reports of erectile dysfunction were received from the marketing authorisation. In 197 reports the patients recovered, most of them after discontinuation of finasteride. Only 59 reports reported the time to recovery that ranged from 1 day to 4 years with a typical time to recovery of 2-3 months.
One third of patients (200 out of 617) did not recover from this ADR at the time of reporting.
However, it is unknown whether the follow up information was received and the duration of follow up.
The case narratives of two reports only were provided, where the causal association with finasteride cannot be ruled out.

The MAH has not discussed whether there is any mechanistic explanation of erectile dysfunction in association with finasteride and possibility of irreversibility of the disorder. Some animal data showed that DHT-inhibition by finasteride in rats causes replacement of the elastic fibres by disorganized and thick collagenic fibres in tunica albuginea (Asian J Androl 2003; 5: 33-36). It is thought that tunica albuginea plays a major role in the erection mechanism. Studies in human showed that the decrease in elastic fibre concentration in tunica albuginea and changes in microscopic features contribute to erectile dysfunction by impairing the venoocclusive function of the tunica albuginea (Urol Res 1995; 23: 221-6; Br J Urol 1997; 79: 47-53).
The MAH is of opinion that the CCDS contains appropriate information with regard to erectile dysfunction. These ADRs are included to the SPC. Differently from the CCDS the SPC does not contain statement "Resolution of these side effects occurred in men who discontinued therapy with Propecia and in many who continued therapy" which may be misleading. Based on the data provided, the additional warning on possibility of persistence of erectile dysfunctions should be included to the SPC.

8.1.2 Other issues of interest

Testicular cancer
Cumulatively there were 11 serious reports of testicular cancer received. Based on estimated total exposure of approximately 4.2 million patient years of treatment with Propecia from introduction trough 06-Nov-2006, the 11 reports represent an overall reporting rate of 0.2 events per 100,000 patient years. This number is lower than the worldwide incidence of testicular cancer (age-standardised rate of 1.5 cases per 100,000 in 2002).

A review of these 11 reports revealed that in 4 reports there was insufficient information to allow a proper assessment. There were additional 4 reports where the onset of the reported event ranged from 4 months to 2 years, most lacking details of a medical evaluation, concomitant therapy or medical history. In latter 2 of these 4 reports, therapy with finasteride was continued.

Two of the remaining 3 reports were confounded by underlying conditions that are potential risks for the development of testicular cancer, including cryptorchism and HIV infection. The last report was retrospective report of potential exposure to finasteride 1 mg during pregnancy via semen. Testis tumour was diagnosed in the child at age of 12 months.

The MAH concluded that based on clinical review and analysis of spontaneous reports; there is no clear evidence that treatment with finasteride predispose men to the testicular cancer. This issue will continue to be monitored.

Assessor's comment: In the previous PSUR, cumulative number of testicular cancer was 12. The MAH was requested to present cumulative review together with CIOMS forms. However, the short summaries of only 3 reports out of 11 were provided. That makes assessment difficult. The MAH states that estimated reporting rate of testicular cancer is lower than incidence in population. However, it should be borne in mind that due to underreporting, the reporting rate of one or another ADR cannot be directly compared with the incidence of such disorder in population. No conclusion can be made at this point. The MAH should continue to monitor testicular cancer and discuss this issue in forthcoming PSUR (CIOMS forms must be provided!).

Liver function test
In the previous PSUR, a cumulative review of abnormal liver function tests were presented. After evaluation the MAH was asked to include abnormal liver function tests to the SPC. However, the MAH did nor agree to update the SPC and presented a new review on the same issue. This review

includes the reports for both Proscar and Propecia but limits them to the following parameters: serious, positive or negative re-challenge, positive or negative de-challenge.
A total of 84 reports were identified (Proscar, n=41 and Propecia, n=43), reporting rate was 0.43 reports per 100,000 patient years.
Reports were divided to serious, positive or negative re-challenge, positive or negative de-challenge and within the each group classified according to the following categories: no lab values reported, ALT<2x UNL, ALT 2-5x UNL, ALT >5-10x UNL, ALT >10x UNL.
Among serious reports 6 reports concerned Propecia. Case narratives of 4 reports were provided, in 2 of them positive de-challenge was reported.
Two reports of positive re-challenge were reported for Propecia. One report described increase in LFTs not further specified, another one reported increase in GGT more than 5x.
Four reports for Propecia with negative re-challenge were presented. One report reported negative re-challenge for AST (changes from 19 to 13 (after cessation of treatment) and from 16 to 15), but positive re-challenge for ALT and GGT. One report was not discussed because increase in ALT was <2x UNL, no data on re-challenge were presented. One report reported positive de-challenge but negative re-challenge. The last report was confounded with concomitant use of erythromycin.
There were 48 cases reporting positive de-challenge. The number of reports for Proscar and Propecia was not specified. Fourteen case narratives for Propecia were provided.
A total of 15 reports were identified with negative de-challenge. At least 9 reports were associated with Propecia.
The MAD stated that review of these reports indicate that there was no clinical picture in terms of type of liver injury that was seen. In most of the cases, sufficient information was not provided to allow a proper evaluation. Thus, there is no evidence that therapy with finasteride is associated with the development of increased hepatic enzymes.
Furthermore, in the 7-year, placebo controlled NCI Prostate Cancer Prevention Study (PCPS) of over 18,000 men randomised (n=9423 finasteride, N=9459 placebo), only 4 patients (2 in each group) were reported with increased transaminases 2.6-5x UNL and one patient on finasteride with increase up to 2.5x UNL. However, in PCPS liver function tests were not routinely measured.

The MAH respectfully request that the Agency reconsider its position that abnormal LFTs should be added to section 4.8 of the SPC for Propecia.

Assessor's comment: The review presented in the previous PSUR was very confusing and did not contain cumulative data. It is difficult to understand why the review presented in the current PSUR is again limited to some criteria and does not include cumulative data for Propecia. No summary analysis on time to onset or risk factors was presented. The assessor agrees that the type of liver injury cannot be determined from the cases presented. However, the two reports of positive re-challenge and several reports of positive de-challenge do not exclude a possible association with finasteride.
It should be mentioned that increase in ALT was observed in the Phase III studies (1.5% for finasteride vs. 0.8% for placebo). In general this increase was less than 3 times UNL and usually transient.
Information on possible side effects is very important for decision making of treatment. Therefore, the term "abnormal LFTs" should be added to section 4.8 of the SPC for Propecia.

***Comment from Germany**: The assessor's requirement to add abnormal liver function tests to section 4.8 of the SPC is endorsed.*

Psychiatric disorders
Cumulatively 69 reports were received: 50 spontaneous and 19 from the post-marketing surveillance study (Table 4).

Table 4 Reports of psychiatric disorders

	Total	Study reports	Spontaneous reports
Depression	25	19	6
Depression and suicide	5	0	5
Other psychiatric disorders	39	0	39

Nineteen reports were received as part of a post-marketing study (Altomare G, Capella GL. 2002). Depression developed after 9-19 weeks of treatment with finasteride and resolved upon discontinuation of the drug. Two patients accepted reintroduction of the drug, and depression relapsed within 2 weeks. Authors concluded that further studies should are needed to confirm these observations.

Six spontaneous reports describing depression were received. Two cases out of six reported positive de-challenge after discontinuation of finasteride. In 2 cases finasteride was continued and the patients did not recover. Two other cases did not contain information on action taken and outcome.
Five reports described depression and suicide. Limited information makes evaluation of these cases difficult.

Other psychiatric disorders were reported in 39 cases: 23 of them concerned libido and orgasm changes and were not discussed. The remaining 14 reports described different psychiatric disorders. There was no pattern among the reported events that would suggest a causal association with finasteride.

The MAH concluded that there is not clear evidence of causal association between finasteride and the development of psychiatric disorders. The company will continue to monitor psychiatric disorders.

Assessor's comment: The MAH has presented pathophysiology of depression but did not mention a possible influence of finasteride on the functions of CNS. The cases (n=17) described in the PMS and two spontaneous cases reported a positive de-challenge, and two cases in PMS reported a positive re-challenge. Rahimi-Ardabili B et al. published the results of a prospective study investigating finasteride induced depression. The authors showed that treatment with finasteride increased both Beck Depression Scale and Hospital Anxiety and Depression Scale scores significantly. They discussed that 5 alfa-reductase is a critical enzyme in the conversion of several steroids such as testosterone, progesterone, aldosterone and corticosterone in the brain. The enzyme converts progesterone to dihydroprogesterone with is further converted to allopregnanolone decreased levels of which is found to be associated with depressive disorders. The authors concluded that this preliminary study suggests that finasteride might induce depressive symptoms. The MAH should discuss this issue and the possible mechanisms in the next PSUR and consider updating the SPC.

8.2 ***Drug interactions***

One report was received. It concerned possible interaction between Propecia and escitalopram that resulted in decreased efficacy of finasteride. It should be noticed that alopecia is a listed adverse reaction of escitalopram.

Assessor's comment: No new safety signal was identify from this report.

8.3 ***Overdose and treatment***

There were 6 reports of overdose received. There were 4 reports in children accidentally ingesting finasteride, 2 reports of prescribed overdose, and 1 report of intentional overdose. On report of

prescribed overdose concerned a 10-year-old boy who was placed on therapy with finasteride and experienced hypertrophy of his breast.

Assessor's comment: These cases do not contain new information on overdose of finasteride. The case reporting the use of finasteride in child does not describe overdose but off-label use. The current SPC contains warning that finasteride should not be used in children.

8.4 ***Drug Abuse or Misuse***

During the period under review 42 reports of misuse were received. Of the 42 reports, 30 involved an alternative dosing schedule, and 11 involved female exposure to therapy with finasteride, and 1 report involved a dispensing error.

Cumulatively there were 137 reports of drug misuse including off-label use. Of these 137 reports, there were 40 reports of splitting and/or crushing tablets, 70 reports of off-label use in females, and 27 reports of other medication errors.

Of the 40 reports of splitting and/or crushing tablets, 36 contained non-serious ADRs, and 4 contained serious events. However, from the cases presented it is unclear which events were serious (it was stated that serious events are in bold, but no event was bolded) and unlisted.

Of the 70 reports of off-label use in females, 63 contained non-serious ADRs, and 7 contained serious ADRs. The MAH concluded that Propecia is not indicated in women and that the CCDS contains adequate information about that.

Twenty-seven reports of other medication errors described primarily alternative dosing schedules. Twenty three reports contained non-serious ADRs.

Assessor's comment: Quite a number of case reports concerned off-label use and alternative dosage of finasteride. The drug is prescribed off-labelled for women and adolescents, despite the warning that "Propecia should not be used in children" as well as information on lack of efficacy in postmenopausal women contained in the SPC. The SPC contains also wording that there is no evidence that an increase in dosage will result in increased efficacy. However, the MAH is asked to suggest risk minimization activities for off-label use pg Propecia.

8.5 ***Death***

One report with fatal outcome was received. It concerned a 76 year old male with pesticide angina pectoris, other co-morbidities and with acute leukaemia diagnosed while on finasteride, 1 mg therapy.

Assessor's comment: No new safety signal was identify from this report.

8.6 ***Special patient groups***

Not information provided.

Assessor's comment: There were several reports of finasteride use in children. In the next PSUR a cumulative review of all reports of finasteride use in children (younger that 18 years) should be presented.

8.7 ***Pregnancy and lactation***

During the period of this PSUR, 30 new reports and new information for 1 previous report of drug exposure during pregnancy were received. Of the 30 new reports, 19 reports were prospective (14

exposure via semen, 3 dermal and 2 oral exposure), and 11 reports were retrospective (9 exposure via semen, and 2 oral exposure). The outcomes of prospective reports of pregnancy are not known yet. The outcomes reported in retrospective reports were as follows: exposure via semen: induced abortion (n=2, one due to foetal aplasia), elective abortion, miscarriage, female infant with symbrachydactyly, full-term infant with ambiguous deformed genitalia, and male baby with arteriovenous malformation. No information on outcome was provided in three reports.

Cumulative review of pregnancy with known outcome for Propecia was provided.
A total of 299 spontaneous and study reports of potential exposure to finasteride 1 and 0.2 mg during pregnancy and lactation were received from the market introduction. The outcome was provided in 161 reports (Table 2)

Table 2 The numbers of prospective and retrospective cases with known outcome reported for finasteride 0.2 and 1 mg; divided upon routes of exposure and type of outcome

Exposure route	**Type of outcome**							
	Normal newborn		**Elective abortion**		**Spontaneous abortion**		**Other adverse outcome**	
Prospective reports								
	Study	*Spontan*	*Study*	*Spontan*	*Study*	*Spontan*	*Study*	*Spontan*
Semen	28	23	5 (?)*	2	4	3	0	1
Oral	-	3	-	2	-	0	-	0
Dermal	-	5	-	2	-	0	-	0
Retrospective reports								
	Study	*Spontan*	*Study*	*Spontan*	*Study*	*Spontan*	*Study*	*Spontan*
Semen	11	2	5 (?)*	5	2	37	5	20
Oral	-	0	-	0	-	0	-	0
Dermal	-	0	-	0	-	1	-	0

* There were 5 elective abortions listed to be from study reports and semen exposure. It was not stated whether these were prospective or retrospective.

Table 3 Summary of cases reporting any male urogenital abnormality, following exposure to finasteride 0.2, 1 mg via semen

Case number	**Exposure**	**Description of case**
Prospective		
0409GBR00189	GW 18-approx. 30	Male baby who at age 3-4 w. developed urinary tract infection. A 6 w. check noted that the boy had small bilateral hydroceles. Unknown relation w. finasteride
Retrospective, spontaneous		
99110293	Entire pregnancy	Premature male infant born (GW 27) with usual type, mild stage 1 (distal) hypospadias. Baby also diagnosed with two inguinal hernias and undescended testicles. Due to prematurity, born with respiratory distress, which required mechanical ventilation.
0201USA01826	Finasteride was stopped 3-4 weeks prior to GW 1	Male baby born with undescended testicle, congenital chordee and hypospadias
0208USA03286	GW 1 through part of first trimester	Male baby born with ambiguous genitalia and hypospadias. Genetic testing showed that all child's Y-chromosomes were abnormal. An endocrinologist did not believe it was related to finasteride
0303USA01891	Not reported	Male baby born with pectus excavatum and megametus
0501USA01532	Not reported	Male baby born with hypospadias
0507FRA00004	About GW 2 to end of	Male baby born with hypospadias and micropenis. Deficiency

	pregnancy	of 5-alpha reductase excluded.
0403CAN00068	Since approx. 1999	Male baby born in 2001/02 with undescended testicle, which had to be removed as it was atrophic
0502GBR00145	Not reported	Female unaware of partners finasteride intake, and she had not been in contact with crushed or taken any tablet. Experienced premature labour, the doctor concerned about baby's genitalia as it was unclear if it was a boy or a girl
0602USA04565	About GW 6 to end of pregnancy	Male baby born with ambiguous deformed genitalia, undescended testicles, incomplete urethra, and hypospadias. Infant's dihydrotesterone was normal. Physician tried to rule out 5-alpha reductase deficiency
Retrospective, study		
		none

Table 4 Summary of the Other Adverse Outcome case, **except** those with any male urogenital abnormality, following exposure to finasteride 0.2, 1 mg via semen

Case number	Exposure	Description of case
	Prospective	
		None
Retrospective, spontaneous		
99082265	Not reported	Female infant diagnosed at 10 months with low grade astrocytoma
0409FRA00027	Entire pregnancy	Male born REDA03. In May 04, right testis tumour found. Pathological examination showed testicular yolk sac tumour stage II, which involved whole testis with small teratomatous mature context and vascular embolism. Child recovering from cancer
0501USA00286	From 30 Sept 03 to birth in RE 04	Male baby diagnosed with Prader-Willi syndrome. Physician did not believe it was related to finasteride, but father did.
00061792	Entire pregnancy	Premature infant (GW27-28) with ambiguous genitalia, hyaline membrane disease, markedly small adrenal gland. Chromosome analyses determined a boy. Died 3 days after birth. Evidence of severe intrauterine hypoxic/anoxic damage including small for gestational age sizes, stress involutional changes to many organs and preservation of brain growth. Most likely due to utero-placental insufficiency, although genetic defect could not be excluded.
00120462	1st trimester, duration unknown	'Early abnormality', no tests reported. Lost to follow up.
99060579	1st and 2nd trimester	Foetus had not developed a 4th chamber of her heart. Outcome unknown, lost to follow up.
0206DEU00070	1st trimester, duration unknown	Umbilical cord thickened. Outcome of birth unknown, lost to follow up.
00116099	Entire pregnancy	Six hours afterbirth, apnoea and hypothermia. Blood test showed increased serum pyruvates and lactates. Died about 12 days later with multiple organ failure.
0509CHE00021	Entire pregnancy	Male child born with heart abnormalism
00120725	Male on concomitant 1 mg (started 1999), and 5 mg (unknown date)	Wife had not handled or taken any finasteride tablets. Delivered a baby with numerous birth defects (not further specified).
0512DEU00103	Therapy w. finasteride started in 2001, discontinued in 2002.	Female pregnant in 2002, delivered a female baby in 2003 with malformation in the left hand. Consumer felt it was due to finasteride, two geneticists felt it was not very likely.

The MAH concluded that the analysis of the reports received shows that exposure of pregnant women to semen of men taking finasteride does not constitute a risk to the developing male foetus. The current SPC contains adequate information regarding this issue.

Assessor's comment: The vast majority of reports concerned exposure to finasteride during pregnancy via semen. There is no prospective case reported with urogenital abnormality (excluding one urinary tract infection). Among the retrospective cases, there are 9 reports concerning some kind of urogenital abnormality (excluding one case of testicular tumour and one case with Prader-Willi syndrome).

From prospective cases, there is insufficient data to allow any conclusion regarding an association of exposure to finasteride via semen and adverse pregnancy outcome. It is well established that dihydrotestosterone (DHT) plays an important role in the sexual differentiation and development of male external genitalia. It is also well known that finasteride may, due to its pharmacological properties, adversely affect the development of the external genitals of a male foetus if given to a pregnant woman. Such effects have been demonstrated when finasteride was given to pregnant animals. Thus, given the known consequence of the pharmacological effect of finasteride, an association between finasteride and (some of) the retrospectively reported cases cannot be excluded. On the other hand, of the same reason, reporting bias is obvious. No new safety concern was identified from the data provided. No update to the SPC is warranted at the moment. Exposure to the finasteride during pregnancy should continue to be monitored and addressed in the PSURs.

8.8 ***Long-term treatment***
No data provided.

8.9 ***Lack of efficacy***

Assessor's comment: The MAH did not address this question. In the summary tabulation of unlisted ADR, there were 2 reports of drug effect decreased, 3 reports of drug ineffective and 98 reports of alopecia that may also mean inefficacy of treatment. This makes up to 15% of all reports. The MAH should present cumulative review and discuss this issue in the next PSUR.

9 Commitments of the MAH based on previous PSUR
All questions were discussed in sections above.

10 Differences in the Reference Safety Information (CCSI vs SPC)
Both the CCDS and the SPC were presented; however, the differences were not specified.

11 Conclusion in PSUR
Examination of the data contained within this PSUR support the conclusion that finasteride 0.2 mg and 1 mg is generally well tolerated. Analysis of these data supports the adequacy of the current CCDS in terms of product safety.
The safety profile of finasteride 0.2 mg and 1 mg is closely monitored on a continuing base.

12 Additional comments from MS

Germany: Because of the number of cases on cardiac disorders reported in this PSUR (mostly non-serious, unlisted), this section should be discussed in detail in the next PSUR.

13 Final Conclusion and Recommendation

