NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Member State France:

Product Names in the Referring Member State, if applicable	PROPECIA and generics PROSCAR and generics FYNZUR AVODART and generics COMBODART and generics
Active substance(s)	Finasteride Dutasteride
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holders in the referring Member State	Various

Background

Indication and pharmacology

Propecia (finasteride 1 mg) was first authorised in the EU in 1998 for treatment of men aged 18-41 years with male pattern hair loss in an early stage (androgenetic alopecia) to increase hair growth and prevent further hair loss. A cutaneous spray solution (topical) of finasteride 2.275 mg/mL has been authorised in the same indication in 2020. Finasteride is also authorized in tablets of 5 mg for the symptomatic treatment of benign prostatic hyperplasia (BPH) and for the prevention of urologic events since 1992.

Finasteride is a 4-azasteroid, which inhibits human type II 5- alpha reductase (5-ARI) (present within the hair follicles), an intracellular enzyme that metabolizes testosterone into dihydrotestosterone (DHT), and blocks the peripheral conversion of testosterone to the androgen DHT. In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT. Finasteride inhibits the process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process.

Dutasteride is a dual inhibitor of 5-ARI, it inhibits both type I and type II 5α-reductase isoenzymes and lowers circulating levels of DHT. Dutasteride is authorised in monotherapy or in fixed dose combination with tamsulosine for the symptomatic treatment of BPH. Outside the EEA, dutasteride is also indicated for male pattern hair loss.

Since finasteride can cross the blood-brain barrier, it has the potential to affect 5α-reductase activity in the central nervous system. Non-clinical data suggest that finasteride inhibits conversion of progesterone and testosterone in neuroactive steroids which targets $GABA_A$-

Receptors and may consequently affect brain function and behaviour. Similar mechanism may be hypothesised for dutasteride as a 5-ARIs class effect.

Psychiatric and sexual disorders already known to be related to finasteride 1 mg (Propecia) and dutasteride 0,5 mg (Avodart) and the fixed dose combination dutasteride 0,5 mg + tamsulosine 0,4 mg (Combodart), and corresponding risk minimisation measures at EU level

The first version of Propecia SmPC in 1998 in the EU mentioned sexual disorders - that could lead to mood disorders - in section 4.8 (decreased libido and ejaculation disorder), based on data from clinical trials. Since then, psychiatric adverse reactions have been reported, suggesting a possible link between use and depression or suicidal ideation, and several evaluations of these psychiatric adverse reactions led to updates of the product information:

In 2009, 'persistence of sexual dysfunction after discontinuation of treatment' was included in section 4.8 of Propecia SmPC.

In 2010, 'Depressed mood' was added in section 4.8 of Propecia SmPC based on a large number of case reports on depressive disorders after exposure, including some with a positive dechallenge and rechallenge in healthy men without any known other medications.

In 2014, 'Depressed mood' was also added in section 4.8 of Avodart SmPC and 'Depression' in Combodart SmPC. Persistence of sexual dysfunction after discontinuation of treatment was included in both SmPCs.

In 2017, the ADR 'Depressed mood' was replaced by 'Depression' in section 4.8 of finasteride SmPC taking into account the available spontaneously reported cases and a possible mechanistic explanation (cf. above). A warning in section 4.4 was also added regarding mood alterations (including depressed mood, depression and, less frequently, suicidal ideation). This warning recommends that patients treated with finasteride 1 mg should be monitored for psychiatric symptoms and if these occur, treatment should be discontinued and the patient is advised to seek medical advice.

In the same year, considering the pharmacological plausibility of association between 5-ARIs and depression, and to align SmPCs of dutasteride 0,5 mg with the fixed dose combination dutasteride 0,5 mg + tamsulosine 0,4 mg, 'Depressed mood' was replaced by 'Depression' in section 4.8 of the SmPC of dutasteride 0,5 mg.

In 2018, 'Anxiety' was included in section 4.8 of Propecia SmPC, mainly based on some positive rechallenge cases.

According to Propecia EU RMP, 'Depressive disorders' and 'Persistence of sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders) following discontinuation of Propecia' are important identified risks but there are currently no additional risk minimisation measures and no ongoing or planned additional pharmacovigilance studies. Specific adverse reaction follow-up questionnaires are sent to all HCPs submitting an adverse event report of depression. Safety concerns of PSURs also include these risks as important identified risks.

French actions

Following serious spontaneous cases reported over time at national level with finasteride 1 mg, the French competent authority (ANSM, National Agency for the Safety of Medicines and Health Products) has long been very concerned by the safety profile of finasteride 1 mg, especially as regards psychiatric disorders and sexual dysfunction which can persists after discontinuation of treatment, due to its "aesthetic" indication and target population (healthy young male subjects). Serious cases of psychiatric disorders continue to be reported.

France implemented the following risk minimisation measures at a national level for finasteride 1 mg:

- December 2019:

  - patient information sheet to better inform patients about the risk of psychiatric and sexual disorders associated with finasteride 1 mg.

- July 2022:

  - specific section on the Agency's website to inform the public about finasteride-related risks, including sexual/psychiatric disorders, available via a QR code on the box (https://ansm.sante.fr/dossiers-thematiques/finasteride-1-mg-et-chute-de-cheveux);
  - tool for patients to facilitate the reporting of adverse drug reactions (explanatory video on 'How to report an ADR') available on the Agency's website and via a QR code on the box (https://ansm.sante.fr/dossiers-thematiques/finasteride-1-mg-et-chute-de-cheveux/information-pour-les-patients-traites-par-finasteride-1-mg);

- November 2022:

  - modification of the outer packaging with the insertion of an alert message regarding the risk of adverse reactions, especially psychiatric and sexual disorders, together with the above mentioned QR code;
  - update of the national patient information sheet to add that suicidal ideation can lead to complete suicide and add the QR code mentioned above;

- January 2023:

  - information (via e-mail) to prescribing physicians, as well as non-prescribing physicians likely to manage patients with adverse reactions to finasteride (psychiatrists, endocrinologists, urologists, and andrologists) to draw their attention to consider the possible role of finasteride when patients report psychiatric or sexual disorders. This information was also sent to pharmacists.

Despite these measures, cases of psychiatric disorders (including suicidal ideation) and sexual dysfunction (including long lasting sexual dysfunction that could lead to mood disorders) are still reported to the French agency.

<u>Issues to be considered</u>

New safety data

In July 2024 a worksharing procedure (SE/H/xxxx/WS/728) for Propecia and Proscar (considered as innovator products) concluded with the inclusion of the ADR 'Suicidal ideation' in section 4.8 of Propecia and Proscar SmPC. Even though a causal association between finasteride and suicidal ideation has not been established, it was considered at least a reasonable possibility, given that known ADRs such as sexual disorders, including erectile dysfunction/impotence, depression, decreased libido, may lead to suicidal ideation. This worksharing involved 19 member states including France. Data from the literature and from 468 spontaneous cases of 'suicide and suicidal ideation' events (SMQ Suicide/Self-injury) without risk factors were reviewed. Among those 93 cases reported fatal outcomes, presumably by suicide (cut-off date of 31-Dec-2022). The most frequently reported dosage of finasteride from the fatal cases with or without risk factors was 1 mg (83%).

Psychiatric events are known ADRs ('Anxiety', 'Depression', 'Suicidal ideation' are listed in SmPC) of finasteride 1 mg and 5 mg treatment, and could also be in some patients a consequence of sexual disorders which may persist long after treatment discontinuation (i.e. 'erectile dysfunction', 'sexual dysfunction', 'ejaculation disorder').

Need for benefit/risk reassessment

France is of the view that the fact that 'Suicidal ideation' was recently recognized as an ADR, along with the reporting of cases of completed suicide, seriously alter the risk profile of finasteride. Considering that androgenetic alopecia, in particular in an early stage, is not a serious condition ('aesthetic indication') and that finasteride 1 mg is indicated for healthy young male subjects, France considers that the impact of the risk of suicidal ideation and possible risk of suicide on the B/R balance of finasteride 1 mg should be reassessed.

In addition, given that this worksharing concerned Organon's products only (Propecia and Proscar), did not cover other formulations, did not concern all EU Member States, did not concern dutasteride products and that the scope of the procedure only referred to the addition of a new ADR, France considers that a referral procedure is warranted.

Topical finasteride 2.275 mg/ml has the same indication as finasteride 1 mg (androgenetic alopecia in men aged 18-41 years). Although it has lower systemic absorption than oral finasteride (mean maximum plasma finasteride concentrations following topical application are >100 times lower than after 1 mg once daily oral finasteride administration), and suicidal ideation is not a known ADR of finasteride in this formulation (no data on suicidality have been reported so far), France considers it is questionable whether the risk of suicide is comparable for the topical formulation, and whether it has the same impact on the B/R balance since the risk cannot be ruled out. Therefore it should be included in this referral.

Finally, considering that finasteride 5 mg and dutasteride 0,5 mg have a different indication (benign prostatic hyperplasia) intended for a different population (elderly patients), their benefit-risk balance may not be impacted in the same way. However, taking into account that these medicinal products contain an active substance with a similar mechanism of action, similar adverse reactions are expected and therefore both finasteride 5 mg and dutasteride 0,5 mg should be included in the scope of this referral to ensure a comprehensive assessment (mechanistic hypothesis, population influence, indications, etc.) as already performed by other Health authorities in non-EEA countries (e.g. UK, Canada, Japan, USA).

Overall, France considers that all available data on suicidal ideation and suicide related to finasteride- and dutasteride-containing products should be reviewed, as well as the impact of these possible risks on the benefit-risk balance of those products.

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed Alexandre DE LA COLOMBE DE LA VOLPILIERE Signature numérique de Alexandre DE LA COLOMBE DE LA VOLPILIERE Date : 2024.09.13 16:58:01 +02'00' Date