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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

INNs: finasteride and dutasteride

Procedure number: EMEA/H/A-31/1539

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Finasteride- and dutasteride-containing medicinal products have a known risk of psychiatric disorders. In 2024, suicidal ideation was added to the product information of the originator products containing finasteride 1 mg (Propecia) and finasteride 5 mg (Proscar) for oral use as a possible adverse drug reaction with a frequency 'not known'.

Considering this safety information, that cases of completed suicide have been reported with finasteride, and since both finasteride and dutasteride belong to the same class of drugs (5-alpha-reductase inhibitors) and share a similar mechanism of action, the French national competent authority (ANSM) considered that all available data on suicidal ideation and suicide related to these medicines should be reviewed.

On 13 September 2024, ANSM triggered a procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested PRAC to assess the impact of the above concerns on the benefit-risk balance of finasteride- and dutasteride-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Finasteride and dutasteride belong to the class of 5-alpha reductase inhibitors (5-ARI). 5-ARI block the 5-alpha-reductase enzyme, reducing the conversion of testosterone to its active form, dihydrotestosterone (DHT). DHT plays an important role in several diseases or conditions, including male androgenetic alopecia and benign prostate hyperplasia (Al-Horani et al., 2024; Marihart et al., 2005).

Finasteride 1 mg tablet was authorised in the European Union (EU) in 1998 and is available for oral use for the treatment of men aged 18-41 years with male pattern hair loss in an early stage (also known as male androgenetic alopecia). Since 2020, finasteride is also authorised for topical use, specifically for cutaneous use as a cutaneous spray solution at the strength of 2.275 mg/mL with the same indication. For the purpose of this report, the terms 'topical use' and 'cutaneous use' are used interchangeably. In addition, finasteride is authorised at the strength of 5 mg for oral use for the symptomatic treatment of benign prostate hyperplasia and for the prevention of urologic events since 1992. Finasteride 5 mg for oral use is also authorised in combination with sildenafil, a phosphodiesterase 5 (PDE-5) inhibitor, or tamsulosin, an alpha-blocker, in the same indications.

In the EU, dutasteride 0.5 mg capsule was authorised in 2001 for oral use and is indicated for the management of symptomatic benign prostate hyperplasia to alleviate symptoms and decrease the risk of acute urinary retention and the potential need for surgery. Dutasteride is also authorised in combination with tamsulosin for the same indication.

Based on the data assessed in the procedure, the cumulative patient exposure worldwide is estimated to 270,756,672.5 patient-years for medicinal products containing finasteride used as monotherapy and to 82,197,163.81 patient-years for medicinal products containing dutasteride used as monotherapy. Based on data from the latest periodic safety update report single assessment (PSUSA) procedure for finasteride (data lock point: 31 August 2023), the cumulative patient exposure for medicinal products containing finasteride 5 mg for oral use is estimated to be three times higher than for medicinal products containing finasteride 1 mg for oral use.

While the risk of psychiatric disorders was already known for finasteride-containing medicinal products, a worksharing variation procedure (SE/H/xxxx/WS/728) concluded in 2024 on the inclusion of suicidal ideation as an adverse drug reaction to the product information of the originator medicinal products containing finasteride 1 mg (Propecia) and finasteride 5 mg (Proscar) for oral use with a frequency 'not known'.

In France, risk minimisation measures relating to the risks of psychiatric and sexual disorders associated with finasteride 1 mg for oral use have been implemented since 2019 (including a warning on the outer packaging, a patient information sheet, a dedicated section on the national agency website and direct email information to physicians). However, cases of psychiatric disorders, including suicidal ideation and sexual dysfunction, are still reported at the national level. Therefore, France considered it necessary to reassess all available data on suicidal ideation and suicide related to medicinal products containing finasteride 1 mg for oral use and their impact on the benefit-risk balance of these medicinal products. France also considered that the scope of the review should include medicinal products containing finasteride 5 mg, as well as dutasteride-containing products in view of the mechanism of action common to the class of 5-ARI.

On 13 September 2024, ANSM triggered the current procedure requesting PRAC to assess the impact of the above concerns on the benefit-risk balance of finasteride- and dutasteride-containing medicinal products and to issue a recommendation accordingly.

PRAC considered all available data in relation to the safety concerns of suicidal ideation and behaviours associated with the use of finasteride- and dutasteride-containing medicinal products, including clinical and non-clinical data, data from spontaneous reporting and the literature. PRAC also considered interventions from third parties. A summary of the most relevant information is included below.

Clinical aspects and characterisation of the risk

Finasteride is a competitive inhibitor of type II 5-alpha-reductase (5-AR), suppressing serum DHT by approximately 70% from baseline. Dutasteride targets both isoforms of this enzyme, types I and II, making it a potent agent in reducing DHT levels to more than 90% (Roehrborn et al., 2004; Marihart et al., 2005). The type I 5-AR isozyme is primarily found in skin-related sebaceous glands, sweat glands, and keratinocytes, synthesizing about 33% of circulating DHT. Type II 5-AR is the predominant isoform within the prostate and it is found in other male genital tract-associated structures such as the epididymis, vas deferens, and seminal vesicles, as well as extraprostatic sites, namely hair follicles and liver, accounting for about 66% of serum DHT production (Al-Horani et al., 2024).

Benign prostate hyperplasia refers to the non-malignant enlargement or hyperplasia of prostate tissue and is a common cause of lower urinary tract symptoms (LUTS) in older men. DHT seems to be the primary androgen responsible for the prostate gland's maturation during development and its growth later in life through the normal masculinisation of external genitalia. DHT can also lead to benign prostate hyperplasia by modulating genes responsible for cell proliferation. Reducing the serum DHT levels increases epithelial apoptosis and decreases prostatic volume (Al-Horani et al., 2024).

Male androgenetic alopecia (also known as male pattern hair loss or male balding) is a common, progressive form of hair loss characterised by a gradual loss of hair preferentially affecting the temples, vertex and mid frontal scalp (Asfour et al., 2023). The pathophysiology of male androgenetic alopecia involves a complex interplay between genetic predisposition and androgenic hormones, particularly DHT, which binds to androgen receptors in hair follicles. The key pathophysiological features of male androgenetic alopecia are alteration in hair cycle development, follicular miniaturisation, and inflammation. As a result, the hairs become unable to grow long or thick enough to reach the surface of the skin, often leaving behind visibly empty follicular pores (Asfour et al., 2023).

Psychological burden constitutes a major component of the morbidity associated with male androgenetic alopecia, as evidenced by several studies reporting negative self-perception in individuals experiencing hair loss (Cash et al., 1992; Budd et al., 2000; Huang et al., 2021; Tabolli et al., 2013). Nevertheless, most affected men cope well with male androgenetic alopecia, without any significant impact on their psychosocial function. Thus, those who seek treatment to minimise further hair loss and for regrowth are likely to be in a greater emotional distress (Asfour et al., 2023).

Suicidal ideation refers to thinking about, considering, or planning suicide. The ideation exists on a spectrum of intensity, beginning with a general desire to die that lacks any concrete method, plan, intention, or action, and progressing to active suicidal ideation, which involves a detailed plan and a determined intent to act on those thoughts. Suicide is defined as death caused by self-directed injurious behaviour with the intent to die as a result of that behaviour. Additionally, a suicide attempt is a non-fatal, self-directed, potentially injurious behaviour with the intent to die as a result of the behaviour, which may or may not result in injury (Harmer et al., 2024).

Mechanism of suicide related events

One plausible mechanism linking 5-ARI to neuropsychiatric side effects includes alterations in neuroactive steroids, which have anticonvulsant, antidepressant, and anxiolytic properties. 5-ARI inhibit the enzyme 5-AR which plays a role in steroid hormone pathway, which in turn affect not only the peripheral formation of DHT but also different neuroactive steroids that act on the gamma-aminobutyric acid (GABA)-A receptors. Finasteride primarily inhibits type II 5-AR, while dutasteride inhibits both type I and type II 5-AR, which are differentially expressed in the brain (Azzouni et al., 2012).

Several publications focused on neuroactive steroids such as allopregnanolone. Duskova et al. (2009) analysed the steroid hormone profiles of 12 patients treated with finasteride 1 mg for four months, revealing a gradual decrease in DHT and other neuroactive steroids known to modulate the inhibitory GABA-A receptors, including allopregnanolone. Melcangi et al. (2013) evaluated neuroactive steroid levels in three former finasteride patients who experienced sexual side effects and anxious/depressive symptomatology that persisted after treatment discontinuation, confirming decreased levels of allopregnanolone and DHT, and increased levels of testosterone and 17b-estradiol.

Alterations in neuroactive steroids can lead to dysfunction of the dopaminergic system, reduced hippocampal neurogenesis, increased neuroinflammation, alterations in the hypothalamic pituitary adrenal axis, and epigenetic modification of proteins involved in the regulation of steroid and pyrimidine metabolism, as well as GABAergic neurotransmission in the nucleus accumbens (Saengmearnuparp et al., 2021).

Based on the scientific literature and on non-clinical data (see section 2.3.), PRAC noted that neurosteroids and their metabolites may play a central role in the development of depression and suicidal ideation, although the complete specific effects of 5-ARI have not yet been fully characterised.

2.2. Safety aspects

2.2.1. Post marketing safety data from EudraVigilance

At the request of PRAC, EMA provided a line listing from EudraVigilance (EV) of cases of suicide and related terms, using the Standardised MedDRA Query (SMQ) 'suicide/self-injury' reported with finasteride- or dutasteride-containing medicinal products received worldwide up to 31 October 2024. The listing comprised all report types (spontaneous, study reports, other, and unknown/not available to the sender), limited to cases where finasteride- or dutasteride-containing medicinal product(s) were

considered suspect or interacting. The WHO-UMC system for standardised case causality assessment was used. According to its criteria, a probable case is an event with a reasonable time relationship to medicine intake, unlikely to be attributed to the patient's disease or by the use of other drugs, showing a clinically reasonable response to withdrawal, and not requiring rechallenge. A possible case is an event with a reasonable time relationship to drug intake, but which could also be explained by the patient's disease or by the use of other drugs, and where information on drug withdrawal may be lacking or unclear.

Overall, 739 cases were identified, from which 16 cases (+ 1 duplicate) were assessed as probably related, 309 cases as possibly related, while the remaining cases were assessed as 'not assessable' mainly due to a lack of relevant information (346), as unlikely (49) or unrelated (18). Amongst the 325 probable or possible cases identified, 313 cases were reported with finasteride and 13 with dutasteride (1 case reported the use of both finasteride and dutasteride).

Out of the unique 16 cases assessed as probably related, 15 cases involved oral finasteride, including 14 reported with finasteride 1 mg and one case with finasteride 5 mg. The other case assessed as probably related was reported with dutasteride. Amongst these probable cases, a positive dechallenge was found in 11 cases involving finasteride 1 mg, the case involving finasteride 5 mg and the case involving dutasteride. No case of rechallenge was observed. Regarding the possibly related cases, 298 involved finasteride (either as 1 mg, 5 mg, or with strength not specified). These included 248 cases that specifically reported the use of finasteride 1 mg and 15 cases that reported finasteride 5 mg.

Amongst the 16 unique probable cases, all were serious. Where seriousness criteria were documented, it was found that one case resulted in death, one case required hospitalisation, and one case involved life-threatening events (all three cases reported with finasteride 1 mg). Out of the 309 possible cases, 297 were reported as serious and 12 cases as non-serious. Where provided, death was reported in 25 cases (21 reported finasteride use, 3 cases dutasteride use and one case reported the use of both active substances in the male androgenetic alopecia indication). Additionally, 58 cases required hospitalisation (57 of them reported with the use of finasteride), and 41 cases were considered life-threatening (all reported with finasteride use).

The most reported indication in these cases was alopecia and related terms (262: alopecia; androgenetic alopecia; alopecia, androgenetic alopecia; diffuse alopecia; alopecia, ill-defined disorder; alopecia, alopecia areata; alopecia, prophylaxis; alopecia, benign prostatic hyperplasia, prostatic disorder, urine flow decreased, alopecia, androgenetic alopecia, benign prostatic hyperplasia). Indications related to benign prostate hyperplasia were reported in 24 cases (benign prostatic hyperplasia; prostatomegaly; micturition disorder; alopecia, benign prostatic hyperplasia, prostatic disorder, urine flow decreased; alopecia, androgenetic alopecia, benign prostatic hyperplasia prostatitis; dysuria). Two cases were reported for both alopecia and benign prostate hyperplasia. Information about the indication was not provided in 33 cases.

None of the 16 unique probable cases reported off-label use. However, 40 possibly related cases reported off-label use (39 cases for finasteride and 1 for dutasteride). In the case of off-label use reported with dutasteride, the latter was used in the indication of male androgenetic alopecia. In all 39 cases reported with finasteride except one and where the indication was provided, finasteride was taken in the indication of male androgenetic alopecia. The remaining case described off-label use for the treatment of hirsutism and polycystic ovarian syndrome in a female patient. In addition, a pattern of quartering finasteride 5 mg tablet into a dose of 1.25 mg was identified (18 cases). There were also individual cases involving patients under 18 or the use of a dose lower than finasteride 1 mg tablet.

The route of administration was reported in 271 cases. Except for one case, all of them reported the oral route of administration. In one case, both the oral and topical routes of administration were reported with finasteride.

Patient age was provided for 202 cases out of 325. 193 cases were reported with finasteride with a median age of 30 years old. For the 10 cases identified with dutasteride, the median age was 57 years. One case reported the use of both finasteride and dutasteride.

The most common preferred term (PT) reported from the SMQ 'suicide/self-injury' was 'suicidal ideation' reported in 261 possibly related cases and in all the probably related cases. The PT 'completed suicide' or 'suicide attempt' was reported in 37 cases assessed as possibly related and 2 probably related cases. Among the 39 cases of completed suicide and suicide attempt, 32 cases concerned the indication of alopecia, and 6 cases of benign prostate hyperplasia. In one case, finasteride was administered for an unknown indication. Additionally, in 16 cases, the PT 'depression suicidal' (16/325) was reported. In 8 of the 39 cases, psychiatric disorder was reported in medical history.

In the cases reporting completed suicide and suicide attempts, no specific pattern of common risk factor(s) was identified.

There was also a significant number of PTs pertaining to the risk of sexual dysfunction observed in the analysed cases. These included the following PTs: erectile dysfunction (198), loss of libido (109), sexual dysfunction (102), libido decreased (73), ejaculation disorder (58). All possible and probable cases were manually screened to identify patterns of combination between sexual and psychiatric adverse drug reactions, despite drug withdrawal. This pattern was identified in 187 (6 probable, 181 possible) out of 325 cases.

2.2.2. Literature data

The scientific literature was reviewed to identify available evidence related to finasteride- and dutasteride-containing medicinal products and the risk of suicide ideation and behaviours.

Pompili et al. (2021) conducted a systematic review of 14 publications primarily focusing on the risk of depression associated with finasteride in patients with male androgenetic alopecia or benign prostate hyperplasia, although reports involving suicidal ideation, attempts, or suicides were also included. The risk of suicidal ideation or behaviour was reported in five of the publications. At crude pooled rates, the suicidal risk was 21.2% (95% confidence interval (CI) 21.0%–21.5%) with finasteride vs 14.0% (95% CI 13.8%–14.3%) without finasteride ($p < 0.0001$). Random-effects meta-analysis yielded an odds ratio [OR] of 2.14 (1.40–3.27) ($p < 0.0001$). In addition, the risk of suicidal ideation or behaviour was greater with vs without finasteride (21.2% [21.0%–21.5%] vs 14.0% [13.8%–14.2%], $p < 0.0001$), and the risk of sustained sexual dysfunction was high (60.1% [37.3%–82.9%]). However, pooled rates on suicidal ideation or behaviour need to be carefully interpreted, since only a limited number of reports (n=5) were available.

Uleri et al. (2024) also conducted a systematic review and meta-analysis involving 2,213,600 patients that investigated the association between 5-ARI use and the potential risks of depression and suicide. The study found no statistically significant association between 5-ARI exposure and the risk of depression (adjusted hazard ratio [HR] 1.30; 95% CI 0.85–2.00; $p = 0.23$) or suicide (adjusted HR 1.30; 95% CI 0.65–2.61; $p = 0.45$). Similar results were obtained in subgroup analyses for finasteride and dutasteride. Moreover, when restricting the analysis to patients without a prior diagnosis of depression, similar findings were observed (adjusted HR 1.00; 95% CI 0.68–1.46; $p = 0.98$).

However, the results present limitations which include a significant heterogeneity of the studies part of the review and a lack of high-quality data.

There were also various pharmacoepidemiology and pharmacovigilance studies that investigated suicidal ideation and suicide, as well as sexual dysfunction in individuals using 5-ARI.

Ali et al. (2015) conducted a retrospective pharmacovigilance disproportionality analysis to measure low-dose finasteride-related adverse events by using data retrieved from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database. The data spanned from 1998 to 2013 and included men aged 18-45 years. From a total of 4,910 reports, 577 (11.8%) of them reported persistent sexual dysfunction and 39 (7.9%) suicidal ideation in young men using finasteride 1 mg in the male androgenetic alopecia indication. 34 (87.2%) of the 39 men with suicidal ideation also experienced sexual dysfunction. While disproportional reporting in suicidal ideation events was noted, it did not reach a signal threshold.

Baas et al. (2018) also analysed reports (n=2,048) from the FAERS database from April 2011 to October 2014. Finasteride 1 mg had an increased frequency of reported adverse events when compared to finasteride 5 mg (1,581 reporting finasteride 1 mg, 240 finasteride 5 mg, and 226 unreported doses). The adverse events reported with finasteride 1 mg included erectile dysfunction (56.2%), diminished libido (41.9%), and ejaculatory complaints (25.6%). There were also adverse events of psychological complaints reported for finasteride 1 mg, including depression and anxiety (47.5%), and suicidal thoughts (2.5%). Since this study is solely based on spontaneous reports, important limitations were noted including causality uncertainties, underreporting and/or stimulated reporting by media attention and labelling changes.

Nguyen et al. (2021) conducted a pharmacovigilance case-noncase study using disproportionality analysis to investigate the association of suicidality (ideation, attempt, and completed suicide) and psychological adverse events (depression and anxiety) with finasteride use. This study included 3,282 individual case safety reports retrieved from VigiBase between 1993 and 2019, from which 356 cases of suicidality were identified and 2,926 cases of psychological adverse events. Amongst the cases with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18-44 years. A significant disproportionality signal for suicidality (reporting odds ratio [ROR] 1.63; 95% CI 1.47-1.81) and psychological adverse events (ROR 4.33; 95% CI 4.17-4.49) were identified in finasteride users. When stratified by age and indication, there was also a significant disproportionality signal for suicidality in younger patients less than 45 years old (ROR 3.47; 95% CI 2.90-4.15) and those with alopecia (ROR 2.06; 95% CI 1.81-2.34). These signals were not detected in older patients or patients with benign prostate hyperplasia. Conversely, this disproportionality in reporting of suicidality or psychological adverse events was not observed for medicines with similar indications but different mechanisms of action (tamsulosin and minoxidil) or similar mechanisms of action and adverse event profiles (dutasteride). The study also found that suicidality and psychological adverse event reports were the highest in 2015 to 2019 (81.5% and 78.8%, respectively). Sensitivity analyses showed a disproportionate signal of reporting after 2012 (ROR 2.13; 95% CI 1.91-2.39), following the widespread publicisation of a potential link between finasteride and psychological morbidity. This suggests a reporting bias of stimulated reporting during these years.

A recent study by Gupta et al. (2025) used data from the FAERS database to evaluate the association of depression and suicide with oral finasteride (1 mg and 5 mg) in males. The authors found no significant link between oral finasteride and reports of depression or suicide from 2006 to 2011. However, similarly to the findings of Nguyen et al. (2021), a significant number of such reports emerged during the period 2013-2018 (ROR 2.8; $p < 0.05$) and 2019-2023 (ROR 5.0; $p < 0.05$), considered as possibly related to an increased awareness of these adverse events following their publicisation in 2012.

Pennap et al. (2024) compared the risk of intentional self-harm and suicide in men aged 65 years or older using 5-ARI and alpha-blockers for benign prostate hyperplasia. This retrospective observational study included a large study population of 64,352 users of dutasteride 0.5 mg and 117,089 users of finasteride 5 mg. The results showed that 5-ARI use was not associated with an increased risk for intentional self-harm or suicide compared to alpha-blocker use in older men with benign prostate hyperplasia (HR 0.88; 95% CI 0.62-1.25 and HR 0.82; 95% CI 0.54-1.24, respectively).

Welk et al. (2017) conducted a large population-based, retrospective, matched cohort study using linked administrative data for 93,197 men aged 66 years or older in Canada who initiated a new prescription for a 5-ARI. The authors found no association between 5-ARI use and an increased risk of suicide in this population (HR 0.88; 95%CI 0.53-1.45) compared to unexposed men. The risk of self-harm was significantly increased during the initial 18 months after 5-ARI initiation (HR 1.88; 95%CI 1.34-2.64), but not thereafter. As for incident depression, patients were at a higher risk during the initial 18 months after 5-ARI initiation (HR 1.94; 95%CI 1.73-2.16), and continued to be elevated, but to a lesser degree for the remainder of the follow-up period (HR 1.22; 95%CI 1.08-1.37). The type of 5-ARI (finasteride or dutasteride) did not significantly modify the observed associations with suicide, self-harm, and depression. Overall, the study did not find any association between 5-ARI use in the benign prostate hyperplasia indication and an increased risk of suicide in a population of men 66 years or older.

Another retrospective cohort study also investigated the potential risk of suicide associated with the 5-ARI use in benign prostate hyperplasia in a population of 51,466 men aged 60 years or older (Kim et al., 2020). Similarly, compared to nonusers, 5-ARI users did not show any increased risk of suicide amongst both subgroups of participants with any psychiatric disorder (HR 0.85; 95% CI 0.49–1.48) and without any psychiatric disorder (HR 1.20; 95% CI 0.73–1.97). The cumulative 5-ARI exposure (during a 7-year follow-up period) was also not associated with an increased risk of suicide (p for trend = 0.543). Similar results were noted with regard to history of depression, where 5-ARI users did not show any increased risk of suicide amongst both subgroups of participants with depression (HR 1.20; 95% CI 0.79–2.47) and without depression (HR 0.95; 95% CI 0.62–1.48). There was no association between 5-ARI use in benign prostate hyperplasia and an increased risk of suicide during the 7-years follow-up period.

Garcia-Argibay et al. (2022) conducted a register-based prospective cohort study in Sweden to investigate the association of 5-ARI use with all-cause dementia, Alzheimer disease, vascular dementia, depression, and suicide. The study included 2,236,876 men aged 50-90 years between July 2005 and December 2018. The authors concluded that there was no association between 5-ARI and suicide (finasteride: HR 1.22; 95% CI 0.99-1.49; dutasteride: HR 0.98; 95%CI 0.62-1.54), but both finasteride and dutasteride were associated with an increased risk for depression (HR 1.61; 95% CI 1.48-1.75 and HR 1.68; 95%CI 1.43-1.96, respectively).

In a nationwide cohort study in France, Laanani et al. (2023) assessed the risk of suicidal behaviours associated with finasteride compared to dutasteride in the benign prostate hyperplasia indication. Men aged 50 years or older initiating finasteride 5 mg or dutasteride 0.5 mg between January 2012 and June 2016 were included and followed until outcome (suicide death identified from death certificate or self-harm hospitalisation), treatment discontinuation or switch, death, or December 2016. The study compared 69,786 finasteride new users to 217,577 dutasteride new users. Overall, finasteride was not associated with an increased risk of any suicidal outcome (HR 1.21; 95% CI 0.87–1.67). However, amongst individuals with a history of mood disorders, finasteride was associated with an increased risk of any suicidal outcome (25 vs 46 events; HR 1.64; 95% CI 1.00–2.68), suicide death (8 versus 10 events; HR 2.71; 95% CI 1.07–6.91), self-harm by violent means (6 vs 6 events; HR 3.11; 95% CI 1.01–9.61), and self-harm with admission to an intensive care unit (7 vs 5 events; HR 3.97; 95% CI

1.26–2.5). Although the study results did not support an increased risk of suicide with finasteride used in benign prostate hyperplasia, an increased risk could not be excluded amongst men with a history of mood disorder. However, these results should be interpreted carefully as they were based on a limited number of events. In addition, a limitation of the study relates to the indication, as patients with male androgenetic alopecia were excluded based on age and the dose of finasteride, which does not rule out any potential off-label use.

Irwig et al. (2012) assessed depressive symptoms and suicidal thoughts in 61 former users of finasteride for the treatment of male androgenetic alopecia who developed persistent sexual side effects (at least 3 months) despite the discontinuation of finasteride and with no baseline sexual dysfunction, or current or past psychiatric conditions. The rates of depressive symptoms were significantly higher in the former finasteride users (75%; 46/61) as compared to the controls (10%; 3/29) ($p < 0.0001$). Moderate or severe depressive symptoms were present in 64% (39/61) of the finasteride group and 0% of the controls. Suicidal thoughts were present in 44% (27/61) of the former finasteride users and in 3% (1/29) of the controls ($p < 0.0001$). However, this study included a small sample size. Another study from the same authors characterised the clinical histories and symptoms reported by a series of 6 suicide victims who all took finasteride for the treatment of male androgenetic alopecia (Irwig et al., 2020). A common pattern of symptoms was reported amongst these cases of completed suicide in the setting of finasteride use: insomnia and persistent sexual dysfunction after medication discontinuation. However, this study presents important limitations including a small sample size, the recruitment of subjects exclusively through volunteered families of individuals who died by suicide, and the possibility of incomplete medical records or undocumented symptoms.

With respect to topical finasteride, the available literature indicates a markedly lower systemic exposure compared to oral finasteride, although it does not completely exclude the risk of systemic adverse drug reactions. The evidence suggests that topical finasteride preferentially inhibits 5-AR in the scalp, leading to a reduced impact on serum DHT concentrations compared to oral finasteride (Piraccini et al., 2022).

2.2.3. Clinical trials data

PRAC reviewed all clinical trials data submitted as part of this procedure concerning suicidal ideation and behaviours. For finasteride-containing medicinal products for oral use, no suicide-related adverse events were reported in any trial treatment groups receiving either finasteride 1 mg or 5 mg, nor were there any reports of suicidal ideation or suicide in follow-up studies. Regarding finasteride for cutaneous use, no mood disorders, depression, or systemic adverse events were reported in any clinical trials. Similarly, for dutasteride-containing medicinal products, the data did not reveal any imbalance in suicidality-related events compared to placebo or other comparator treatment arms.

Based on the available clinical trial data, the findings indicate that there is no evidence supporting an increased risk of suicidality associated with finasteride- or dutasteride-containing medicinal products.

2.2.4. Discussion on safety

Based on the clinical trial data, the review did not identify any new safety concerns related to suicide-related adverse events. Although suicidality-related adverse events were reported in clinical trials with dutasteride and dutasteride fixed-dose combination with tamsulosin, no imbalance was observed when compared to placebo or other comparator treatment arms. Similarly, no suicide-related adverse event was reported in clinical trials involving finasteride 1 mg for oral use, finasteride 5 mg for oral use, fixed-dose combination-containing finasteride for oral use, or finasteride for cutaneous use.

In relation to the data from EV, their analysis led to the identification of a total of 739 cases of suicide and related terms for finasteride- or dutasteride-containing medicinal products. Causality was assessed for these cases, resulting in 16 cases being identified as probably related (15 with finasteride, 1 with dutasteride) and 309 as possibly related (297 with finasteride alone, 11 with dutasteride alone and one case reporting both finasteride and dutasteride). There were no cases classified as possibly or probably reported with topical finasteride. The identified cases from the EV analysis indicated a higher risk of suicidal ideation and suicidal behaviours with finasteride for oral use, especially in the indication of male androgenetic alopecia, and only limited evidence for dutasteride. Overall, the evidence regarding completed suicide is too limited. In the cases reporting completed suicide and suicide attempts, no common risk factor could be identified.

Regarding the scientific literature, the studies focused on the benign prostate hyperplasia indication did not identify an increased risk of suicide associated with finasteride or dutasteride (Welk et al., 2017; Kim et al., 2020; Nguyen et al., 2021; Garcia-Argibay et al., 2022; Laanani et al., 2023; Pennap et al., 2024; Uleri et al., 2024). The only exception was the systematic review by Pompili et al., 2021, which included finasteride users from both indications (male androgenetic alopecia and benign prostate hyperplasia) and reported suicide risk at pooled rates. However, the limited study data on the risk of suicide prevented any conclusions about the strength of the evidence.

Several studies suggested an increased risk of suicide in patients with male androgenetic alopecia (Irwig et al., 2012; Ali et al., 2015; Baas et al., 2018; Irwig et al., 2020; Nguyen et al., 2021; Pompili et al., 2021). However, these studies presented major limitations. Pompili et al. (2021) included a limited number of reports on suicidal ideation or behaviours, which hindered the interpretation of the study results. Similarly, the studies by Irwig et al. (2012) and by Irwig et al. (2020) also had a sample size that were too limited. Ali et al. (2015) analysed a large number of spontaneous reports from the FAERS database. However, spontaneous reports are unsuitable for calculating incidence rates. In addition, while disproportional reporting of suicidal ideation events was noted, it did not reach the signal threshold. Of note, Nguyen et al. (2021) and Gupta et al. (2025) observed an increase in reports of psychological and suicidality-related adverse events which they attributed to heightened awareness following the publicisation of these events in 2012, driven by significant media attention. Overall, although studies on male androgenetic alopecia raised concerns, no definitive conclusions could be drawn regarding the risk of suicide.

The lower risk of suicidal ideation observed in patients taking finasteride 5 mg compared to those taking finasteride 1 mg remains unexplained based on the reviewed literature (Welk et al., 2017; Kim et al., 2020; Pennap et al., 2024).

With regard to finasteride for topical use, there was not any relevant study identified in the review regarding the risk of suicidal ideation and behaviours. The recent evidence indicates a lower systemic exposure compared to oral finasteride, although it does not completely exclude a possible risk of systemic adverse drug reactions (Piraccini et al., 2022). Therefore, the MAHs of medicinal products containing finasteride for cutaneous use should provide a review on the risk of suicidal ideation and behaviours in their next periodic safety update report (PSUR) submission.

In terms of risk factors that could increase the risk of developing suicidal ideation and behaviours, the review of the scientific literature did not allow for any definitive conclusions. However, certain publications suggested that sexual dysfunction, sometimes persistent, and history of mood disorders may be possible contributing conditions (Irwig et al, 2012; Ali et al., 2015; Baas et al., 2018; Irwig et al., 2020; Pompili et al., 2021; Laanani et al., 2023). Importantly, Ali et al. (2015) showed that 87.2% (n=34) of men included in their study who were using finasteride 1 mg and experienced suicidal ideation also reported sexual dysfunction, suggesting that sexual dysfunction might be a potential risk of finasteride 1 mg for the treatment of male androgenetic alopecia in young men, and this risk might

contribute to suicidal ideation. Irwig et al. (2012) found that rates of depressive symptoms and suicidal ideation were significantly higher in former finasteride users who developed persistent sexual side effects after treatment discontinuation and had no baseline sexual dysfunction or psychiatric conditions. The same authors also found a pattern of symptoms common to all the 6 cases of finasteride users who committed suicide, including persistent sexual dysfunction after medication discontinuation. However, these studies included a small sample size, among other limitations previously described. Laanani et al. (2023) reported an increased risk of suicidal outcome amongst individuals with a history of mood disorders. Nevertheless, these results were based on a low number of events. On the contrary, Welk et al. (2017) did not observe any significant relationship between prior history of depression or active depression and the risk of suicide. Similarly, the results from Kim et al. (2020) did not show an increased risk of suicide amongst 5-ARI users with underlying depression or any psychiatric disorder.

Overall, the review of the scientific literature on risk factors found the evidence regarding the association between 5-ARI and the risk of suicidal ideation and suicide to be inconclusive. However, when considered alongside with the EV analysis data, the findings suggested that sexual dysfunction may play a contributory role in suicidal ideation in some patients treated with finasteride for the male androgenetic alopecia indication.

Finally, it was noted that cases of off-label use were reported in EV with oral finasteride or dutasteride. The MAHs of medicinal products containing finasteride for oral use or dutasteride should provide a review on the risk of off-label use in their next PSUR submission.

2.3. Non-clinical aspects

Several nonclinical studies have reported neuropsychiatric effects of finasteride in rodents, including depression-like and anxiety-like behaviours, cognitive impairments, and altered gene expression related to mood regulation and neuroplasticity (Sasibhushana et al., 2024). Notably, Giatti et al. (2024) observed changes in the expression of hypothalamic and hippocampal genes in rats that code for proteins involved in pathways such as thyroxine and retinol. Downregulation of these pathways has been linked to learning and memory impairment, aggressive behaviour, neurodegeneration, while also affecting important roles in synaptic plasticity, oxidative stress, inflammation, mood, and neurotransmitter regulation. Additionally, Maurice-Gelinas et al. (2018) reported increased aggressiveness and impulsive behaviours in socially isolated mice treated with finasteride via injection. Frau et al. (2017) showed that intraperitoneal injection of finasteride in rats reduces allopregnanolone levels in brain regions crucial for emotional regulation. Allopregnanolone, a metabolite of progesterone, is a potent ligand of the inhibitory GABA-A receptor, and modulates its activity. In turn, changes in levels of GABA and neuroactive steroids have been linked to depression in clinical studies (Melcangi et al., 2013). These effects were observed primarily at high doses and with non-oral routes of administration (e.g., subcutaneous, intraperitoneal injection). Conversely, two recent studies found antidepressant and anxiolytic effects in both male and female rats (Nayana et al., 2024; Pintana et al., 2024).

However, the findings across studies are inconsistent, and given the high doses used (exceeding the recommended maximum daily dose in humans) and the non-oral routes used, the clinical relevance and translatability of these results to humans remain limited and uncertain.

3. Stakeholders' input

During the procedure, PRAC received over 150 interventions from third parties, with the majority coming from patients or family members. Additionally, interventions were also received from not-for-profit organisations, healthcare professionals and academia.

These interventions concerned individual testimonies or personal views, and/or the sharing of data or information in the form of publications, links to medical journals, pharmacovigilance data, or links to media outlets, social media communities, and websites of not-for-profit and patients organisations, expressing the third parties' views about the efficacy and safety profile of finasteride- and dutasteride-containing products, the medical need of these medicinal products, or the psychological burden associated with male androgenetic alopecia.

These submissions were all considered by PRAC in the context of this review.

4. Benefit-risk balance

PRAC considered all available data in relation to the safety concerns of suicidal ideation and behaviours associated with the use of finasteride- and dutasteride-containing medical products. This included the responses submitted by the marketing authorisation holders in writing, data from clinical trials, from spontaneous reporting and from the literature, non-clinical data as well as interventions from third parties.

Both finasteride and dutasteride belong to the class of 5-ARI. As such, both inhibit the type II 5-AR, which reduces the conversion of testosterone to DHT. The review also noted that 5-ARI may play a role in neuropsychiatric side effects by altering neuroactive steroids and their metabolites. Nevertheless, the neuropsychiatric effects of 5-ARI have not yet been fully characterised.

The non-clinical data reviewed in the context of this procedure did not allow to draw conclusions. The findings across studies are inconsistent, and given the high doses used (higher than the recommended maximum daily dose in humans) and the non-oral routes used, the clinical relevance and translatability of these results to humans remain limited and uncertain.

The efficacy of finasteride- and dutasteride-containing medicinal products in the authorised indications is considered well-established and was not questioned in this procedure. Efficacy was previously demonstrated in multiple studies and no new efficacy data were identified during this review.

Based on the following safety data, conclusions were drawn for each substance and route of administration, leading to an overall benefit-risk balance evaluation for each formulation.

Medicinal products containing finasteride 1 mg, for oral use

Based on the review of the safety data, there were no suicide-related adverse events reported in clinical trials for finasteride 1 mg for oral use.

Of the 739 cases identified in EV for both finasteride and dutasteride, the EV analysis identified 313 unique cases involving oral finasteride (either as 1 mg, 5 mg, or with strength not specified). 15 of them were assessed as probably related, with 14 of these cases reported for finasteride 1 mg, including one fatal case. A positive dechallenge was found in 11 cases involving finasteride 1 mg. Additionally, 298 cases involving oral finasteride (either as 1 mg, 5 mg, or with strength not specified) were assessed as possibly related, including 248 of these cases reporting the use of finasteride 1 mg. These findings are considered supportive of a causal association between oral finasteride and suicidal ideation. Therefore, PRAC confirmed a causal association between oral finasteride and suicidal ideation,

and the latter should be reflected as an adverse drug reaction in the product information of medicinal products containing finasteride 1 mg for oral use with a frequency 'not known'. PRAC noted that the product information of medicinal products containing finasteride 1 mg for oral use already contains a warning on mood alterations including suicidal ideation.

In the literature, studies have suggested an increased risk of suicide with finasteride 1 mg (Irwig et al., 2012; Ali et al., 2015; Baas et al., 2018; Irwig et al., 2020; Nguyen et al., 2021; Pompili et al., 2021). However, significant limitations precluded drawing definitive conclusions.

In terms of risk factors that could increase the risk of developing suicidal ideation and behaviours, the review of the scientific literature did not allow for any definitive conclusions. However, based on the available literature data on male androgenetic alopecia (Ali et al., 2015; Baas et al., 2018, Irwig, 2020; Pompili et al. 2021) alongside with the EV analysis data, the findings suggested that sexual dysfunction may play a contributory role in suicidal ideation in some patients treated with finasteride for the male androgenetic alopecia indication. As a result, PRAC concluded this information should be reflected in the product information of these medicinal products.

PRAC noted that most cases of suicidal ideation were reported following treatment with finasteride for male androgenetic alopecia, despite a considerably larger exposure from treatment for benign prostate hyperplasia. In order to increase awareness amongst patients, PRAC recommended the introduction of a patient card to be made available inside the package to inform patients on the risks of mood alterations including suicidal ideation (already reflected in the product information of medicinal products containing finasteride 1 mg for oral use) as well as of sexual dysfunction which may contribute to these reactions, and providing instructions on the appropriate course of action should these occur.

PRAC concluded that the benefit-risk balance of medicinal products containing finasteride 1 mg for oral use remains favourable subject to the agreed amendments to the product information and risk minimisation measures, as described above.

Medicinal products containing finasteride 5 mg, for oral use

Based on the review of the safety data, there were no suicide-related adverse events reported in clinical trials for finasteride 5 mg.

From the EV analysis, 15 unique cases involving oral finasteride were assessed as probably related, including one case reported with finasteride 5 mg. One probable case reporting a dechallenge was identified for finasteride 5 mg in benign prostate hyperplasia. From the 298 cases involving oral finasteride (either as 1 mg, 5 mg, or with strength not specified) assessed as possibly related, 15 cases reported the use of finasteride 5 mg. These findings are considered supportive of a causal association between oral finasteride and suicidal ideation. Therefore, PRAC confirmed a causal association between oral finasteride and suicidal ideation, and the latter should be reflected as an adverse drug reaction in the product information of medicinal products containing finasteride 5 mg for oral use with a frequency 'not known'. PRAC noted that the product information of medicinal products containing finasteride 5 mg for oral use already contains a warning on mood alterations including suicidal ideation.

In the literature, studies related to benign prostate hyperplasia did not find an increased risk of suicide with finasteride 5 mg (Welk et al., 2017; Nguyen et al., 2021; Garcia-Argibay et al., 2022; Laanani et al., 2023; Pennap et al., 2024; Uleri et al., 2024), except for one study by Pompili et al., 2021, which included finasteride users for both male androgenetic alopecia and benign prostate hyperplasia and reported suicide risk at pooled rates. However, the limited study data on the risk of suicide prevented any conclusions about the strength of the evidence. The lower risk of suicidal ideation observed in

patients taking finasteride 5 mg compared to those taking finasteride 1 mg remains unexplained based on the reviewed literature (Welk et al., 2017; Kim et al., 2020; Pennap et al., 2024).

There was no specific evidence identified for finasteride 5 mg in fixed dose combination with tadalafil or tamsulosin for oral use. As these fixed dose combinations are authorised for the same indication as finasteride 5 mg mono-component, they should follow the same recommendations.

PRAC concluded that the benefit-risk balance of medicinal products containing finasteride 5 mg for oral use remains favourable subject to the agreed amendments to the product information as described above.

Medicinal products containing dutasteride, for oral use

While suicidality-related adverse events were reported in clinical trials with dutasteride and dutasteride fixed dose combination with tamsulosin, no imbalance in suicidality-related events was identified when compared to placebo or other comparator treatment arms.

Of the 739 cases identified in the EV analysis for both finasteride and dutasteride, only one case was reported with dutasteride and assessed as probably related. Additionally, 12 cases were assessed as possibly related to dutasteride, one of which involved the use of both dutasteride and finasteride.

With regard to the literature, no data have been identified indicating an increased risk of suicide associated with dutasteride (Welk et al., 2017; Kim et al., 2020; Garcia-Argibay et al., 2022; Laanani et al., 2023; Pennap et al., 2024; Uleri et al., 2024).

Based on the data reviewed in the procedure, PRAC did not identify sufficient evidence linking suicidal ideation to dutasteride-containing medicinal products. However, based on the common mechanism of action of medicines belonging to the class of 5-ARI, PRAC agreed that a warning referring to a potential risk of mood alterations, including depressed mood, depression and, less frequently, suicidal ideation should be included in the product information of dutasteride-containing medicinal products as a precautionary measure.

There was no specific evidence gathered for dutasteride in fixed dose combination with tamsulosin for oral use. As these medicinal products are authorised for the same indication as dutasteride mono-component, they should follow the same recommendations.

PRAC concluded that the benefit-risk balance of medicinal products containing dutasteride for oral use remains favourable subject to the agreed amendments to the product information as described above.

Medicinal products containing finasteride, for cutaneous use

No relevant literature data have been identified regarding the risk of suicidal ideation and behaviours with topical finasteride.

Additionally, no possible or probable cases linked to finasteride for topical use in monotherapy were identified in the EV analysis (i.e., without the use of finasteride for oral use as a confounder), and no suicide-related adverse events were reported in clinical trials and nonclinical studies.

The literature data demonstrated a lower systemic exposure compared to finasteride for oral use, although it does not fully exclude the risk of systemic adverse drug reactions. PRAC noted that the product information of medicinal products containing finasteride for cutaneous use already includes a warning relating to mood alterations in association with finasteride 1 mg for oral use, including suicidal ideation, as well as the possibility of systemic exposure with finasteride for topical use. In view of the insufficient evidence to confirm a causal association between topical finasteride and the risk of suicidal ideation, and the existing warning in the product information referring to risks of mood alterations

associated with the use of oral finasteride, PRAC agreed that no update to the product information for finasteride for cutaneous use is deemed necessary.

PRAC concluded that the benefit-risk balance of medicinal products containing finasteride for cutaneous use remains favourable, and that no amendment to the product information is warranted based on the data assessed in the procedure.

All finasteride- and dutasteride-containing medicinal products

A direct healthcare professional communication (DHPC) was also agreed, together with a communication plan to inform relevant healthcare professionals of the new measures to minimise the risk of suicidal ideation for finasteride- and dutasteride-containing medicinal products.

5. Summary of new activities and measures

5.1. Risk management

The MAHs for medicinal products containing finasteride 1 mg specifically, should operate a risk management system to be described in a risk management plan (RMP). The RMP should include and reflect the safety concerns and risk minimisations measures listed below, as applicable.

5.1.1. Safety concerns

The Committee considered that suicidal ideation and sexual dysfunction should be added as important identified risks of medicinal products containing finasteride 1 mg for oral use.

5.1.2. Routine risk minimisation measures

PRAC considered that routine risk minimisation measures in the form of updates to the product information of finasteride- and dutasteride-containing medicinal products for oral use was necessary in order to minimise the risks of suicidal ideation and behaviours reported with the use of 5-ARI.

Medicinal products containing finasteride 1 mg, for oral use

PRAC considered that section 4.4 of the SmPC should be updated to reflect that sexual dysfunction, that may contribute to mood alterations, including suicidal ideation, has been reported in some patients. In addition, this section should emphasize that patients should seek medical advice if they experience sexual dysfunction and that discontinuation of treatment should be considered in such cases. PRAC also considered that section 4.8 should be updated to include suicidal ideation as an undesirable effect with a frequency 'not known'.

In addition, the labelling of these medicinal products was also amended to include the agreed wording for a patient card (see below).

Medicinal products containing finasteride 5 mg, for oral use

PRAC considered that section 4.8 of the SmPC should be updated to include suicidal ideation as an undesirable effect with a frequency 'not known'.

Medicinal products containing dutasteride, for oral use

PRAC considered that section 4.4 of the SmPC should be updated to reflect that mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with another oral 5-ARI.

The corresponding sections of the package leaflets should be amended accordingly.

5.1.3. Additional risk minimisation measures

For all medicinal products containing finasteride 1 mg for oral use, PRAC requested the implementation of a patient card to be inserted in the outer packaging. PRAC agreed on a wording informing about the risks of mood alterations, including suicidal ideation, and sexual dysfunction, and advising on the appropriate course of action should such symptoms occur.

5.2. Direct healthcare professional communication and communication plan

PRAC considered that a DHPC was needed to raise awareness of the new recommendations and risk minimisation measures. PRAC recommended that the agreed recommendations and measures are communicated to dermatologists, psychiatrists, general practitioners, and pharmacists.

The Committee agreed on the content of the DHPC together with a communication plan.

All concerned MAHs are encouraged to liaise with the national competent authorities in order to prepare and circulate a single DHPC in each Member State.

6. Conditions to the marketing authorisations

The marketing authorisation holders shall complete the conditions below, within the stated timeframe, and the competent authorities shall ensure that the following is fulfilled:

<u>Medicinal products containing finasteride 1 mg for oral use:</u> The MAHs of medicinal products containing finasteride 1 mg for oral use should operate a risk management system to be described in a risk management plan (RMP) which shall be submitted to the relevant competent authorities. The MAHs should update their RMP or implement a new one to reflect the agreed patient card as an additional risk minimisation measure to address the important identified risks of suicidal ideation and sexual dysfunction.	Within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision, as applicable.

7. Grounds for recommendation

Whereas,

- PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on finasteride- and dutasteride-containing medicinal products.
- PRAC reviewed the available data in relation to suicidal ideation and behaviours associated with the use of finasteride- and dutasteride-containing medicinal products. This included the responses submitted by the marketing authorisation holders in writing, data from clinical trials, spontaneous reporting and literature, non-clinical data as well as interventions by third parties.
- Based on the evaluated cases of suicidal ideation or suicidal behaviours reported with oral finasteride, PRAC confirmed a causal association between oral finasteride and suicidal ideation. Therefore, suicidal ideation should be reflected as an adverse drug reaction in the product

information of all medicinal products containing finasteride 1 mg or finasteride 5 mg for oral use.

- PRAC noted that the product information of all medicinal products containing finasteride 1 mg or finasteride 5 mg for oral use already includes a warning on mood alterations, including suicidal ideation.
- PRAC concluded that sexual dysfunction (a known adverse drug reaction of finasteride) may have a potential contributory role in suicidal ideation in some patients being treated with finasteride 1 mg for oral use and recommended this to be reflected in the product information of these medicinal products.
- PRAC did not identify sufficient evidence linking suicidal ideation to dutasteride-containing medicinal products. However, based on the common mechanism of action of medicines belonging to the class of 5-alpha reductase inhibitors, PRAC agreed that a warning referring to a potential risk of mood alterations, including depressed mood, depression and, less frequently, suicidal ideation should be reflected in the product information of dutasteride-containing medicinal products for oral use as a precautionary measure.
- PRAC noted that most cases of suicidal ideation were reported following treatment with finasteride for androgenetic alopecia, despite a considerably larger exposure from treatment of benign prostate hyperplasia. PRAC therefore recommended a patient card for medicinal products containing finasteride 1 mg for oral use, to be provided inside the package to inform patients on the risks of mood alterations as well as of sexual dysfunction that may contribute to these reactions and provide instructions on the appropriate course of action should these occur. This additional risk minimisation measure should be reflected in a risk management plan.
- PRAC did not identify sufficient evidence linking suicidal ideation to medicinal products containing finasteride for cutaneous use that would prompt an update of the existing warning on mood alterations.

In view of the above, the Committee considers that the benefit-risk balance of medicinal products containing finasteride 1 mg, finasteride 5 mg or dutasteride for oral use remains favourable subject to the agreed amendments to the product information and risk minimisation measures, as applicable.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing finasteride 1 mg, finasteride 5 mg or dutasteride for oral use.

The Committee also considers that the benefit-risk balance of medicinal products containing finasteride for cutaneous use remains favourable and recommends the maintenance of the marketing authorisations.

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Appendix 1

Divergent position to PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1539

Finasteride- and dutasteride-containing medicinal products

Divergent statement

The following PRAC members consider that the benefit-risk balance of medicinal products containing finasteride 1 mg is not favourable based on the following grounds:

Finasteride is a 4-azasteroid, which inhibits human type II 5- alpha reductase (5-ARI). Finasteride 1 mg is indicated in men 18 – 41 years of age for the early stages of androgenetic alopecia. As per the approved indication, finasteride stabilises the process of androgenetic alopecia. Efficacy in bitemporal recession and end-stage hair loss has not been established.

Finasteride 1 mg is available in oral form and has been authorised for more than 25 years in Europe. It has never been approved in Belgium.

In September 2024, France triggered a referral procedure under Article 31 of Directive 2001/83/CE in view of new serious adverse reactions added to SmPC Section 4.8 of medicines containing finasteride 1 mg (Propecia) and 5 mg (Proscar), i.e. "suicidal ideation". The PRAC was specifically asked to assess all available data on suicidal ideation and suicide related to finasteride- and dutasteride-containing products, as well as the impact of these possible risks on the benefit-risk balance of those products.

Based on the reported cases and available relevant literature, the PRAC concluded that a causal relationship between oral finasteride 1 mg and suicidal ideation is confirmed and that a positive benefit-risk balance in the androgenetic alopecia indication remains positive subject to the implementation of adequate risk minimisation measures.

However, the analysis of the referral data has clearly established new aspects of the risks associated with psychiatric disorders and sexual dysfunction. These risks considerably affect the safety profile of oral finasteride 1 mg in light of the approved indication for androgenetic alopecia, which is a benign, aesthetic, and lifelong condition. The expected benefits, i.e. stabilisation of hair loss, in this benign condition do not outweigh the seriousness of these risks, including potential fatal outcomes, in the target population of young healthy patients. The recommended risk minimisation measures including product information updates, patient card and DHPC, will not sufficiently prevent the new important identified risk of suicidal ideation. Indeed, in France, despite the implementation over the years of various risk minimisation measures (including communications via the ANSM's website, patient information sheet, DHPC, boxed warning, and QR code on the outer packaging), serious cases of psychiatric disorders and sexual dysfunction continue to be reported. Moreover, in some patients, these adverse effects may persist for years even after treatment discontinuation and could lead to suicidal ideation. In this context, no effective measures can mitigate these risks.

Therefore, taking into account the above, we consider that the benefit-risk balance of finasteride 1 mg for androgenetic alopecia is negative.

PRAC Members expressing a divergent opinion:

- Jean-Michel Dogné (Belgium)
- Tiphaine Vaillant (France)