Annex II

Scientific conclusions

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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 (MAA) and benign prostate hyperplasia (BPH).

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 MAA). 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 these scientific conclusions, 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 BPH 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 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 BPH 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, France (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.

The PRAC adopted a recommendation on 08 May 2025 which was then considered by CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by PRAC

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-alpha-reductase (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 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 EudraVigilance (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. 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 MAA 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 MAA 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 MAA, despite a considerably larger exposure from treatment for BPH. 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 BPH. 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 BPH did not find an increased risk of suicide with finasteride 5 mg, except for one study which included finasteride users for both MAA and BPH 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.

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.

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.

Grounds for PRAC 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.

CMDh position

Having reviewed the PRAC recommendation, CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, 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 amendments to the product information, risk minimisation measures and condition, as applicable. Therefore, the CMDh 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 CMD 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.