Medicines & Healthcare products Regulatory Agency

Safety review of Finasteride

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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1. Plain Language Summary

Key messages

Finasteride (brand names Propecia, Proscar) is approved in the UK to treat male pattern hair loss (1 mg dose) and benign prostatic enlargement (swollen prostate gland; 5 mg dose).

The MHRA conducted a safety review of finasteride and sought the advice of the independent Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM), relating to the risks associated with finasteride including persistent sexual dysfunction and suicidal thoughts. These are known side effects and are labelled in the product information; however the review was initiated in response to enquiries from patients concerned about the apparent lack of awareness among health care professionals and patients of these side effects.

The MHRA used data from published studies, current product information, the NHS website, other regulatory agencies and testimonials from patients and the public.

The recommendations following this review include the introduction of a patient card in the package detailing some of these side effects and that in some cases, these effects may continue after stopping treatment. A Drug Safety Update (Drug Safety (publishing.service.gov.uk)) has been published to communicate these risks to healthcare professionals. The MHRA has also worked with external organisations who regulate online pharmacies, to improve the guidelines for prescribers.

Introduction to this report

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices, and blood components for transfusion in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The PEAG is an independent group of healthcare professionals and patients which advises the MHRA on the safety, efficacy, and quality of medicines.

This report presents the review of the safety data by the MHRA in 2023, the advice of the PEAG and the steps that the MHRA are taking to implement new safety measures with the support of patients and experts.

More information about finasteride

Finasteride is a medicine used in the management of male pattern hair loss (1 mg dose) and benign prostatic enlargement (5 mg dose). Male pattern hair loss (MPHL), also known as

androgenic alopecia, is the most common cause of hair loss. It is a condition that is related to genes and male sex hormones and results in a specific pattern of hair loss.

Benign (non-cancerous) prostatic enlargement (or hyperplasia, BPH) is a condition in which the flow of urine is blocked due to the swelling of the prostate gland. The prostate gland is located just below the bladder in men and surrounds the top portion of the tube that drains urine from the bladder.

Reasons for this review and how it was done

The MHRA previously completed a safety review into finasteride following concerns raised by patients regarding a lack of awareness of these side effects amongst patients and healthcare professionals. The MHRA issued a Drug Safety Update (DSU) in 2017 (Drug Safety (publishing.service.gov.uk)) regarding reports of depression and suicidal thoughts in men taking finasteride. Finasteride remains under continual monitoring by regulators and market authorisation holders (MAHs), and updates to the product information are implemented as required.

The current safety review was initiated in response to enquiries from patients who are still concerned about the apparent lack of awareness among healthcare professionals and patients of these side effects, The review considered data from the published scientific literature, current product information, the NHS website, other international regulatory agencies and testimonials from patients and the public. The MHRA reviewed the sexual and psychiatric side effects with finasteride.

The MHRA reviewed the risks and presented options on how best to minimise harm to the UK public.

The MHRA sought independent advice on this review from the PEAG, an independent group of experts that advises the Commission on Human Medicines on the safety of medicines. The MHRA's review is presented in this report alongside the advice from the PEAG and actions that the MHRA is taking following this review.

Conclusions of the review

The safety review related to the risks associated with finasteride including persistent sexual dysfunction and suicidal thoughts.

When looking at safety databases, there are increased signals for sexual and psychiatric side effects. It was noted that depression is multifactorial and could be due to underlying psychiatric disorders, the medication itself or related to the sexual side effects of finasteride and/or the condition it is used to treat (BPH and hair loss). Previous European assessments have investigated these adverse effects, with no additional procedures recommended,

although the product information has been updated to include these side effects. Nonetheless, patients have shared their experiences with the MHRA and the devastating effect this can have on their quality of life.

A common theme from the conclusions in the literature review was that healthcare professionals should be explaining potential side effects clearly, completing pre-screening questionnaires to identify patients at risk of adverse effects, and actively monitoring patients.

Another important aspect of this review was regarding the prescribing process for finasteride. The MHRA met with online pharmacies, and while some do have thorough screening and monitoring processes in place, others do not. The MHRA has ongoing activities with other organisations, such as the General Pharmaceutical Council (GPhC), to improve these processes.

The safety review received independent advice from the PEAG, who advised that there may be scope for additional risk minimisation measures to address patient concerns around the lack of awareness of psychiatric side effects and the persistence of sexual side effects in some patients after stopping treatment.

The recommendations following this review include a patient card to be included in the carton detailing some of these side effects and that in some cases, these effects may continue after stopping.

Next steps for the public

If you are a patient on finasteride, please discuss any concerns you have with your healthcare professional or prescriber. The MHRA issued a DSU in April 2024 (Drug Safety (publishing.service.gov.uk)).

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulator of medicines, medical devices, and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality, and efficacy. The Pharmacovigilance Expert Advisory Group (PEAG) advises the MHRA about medicines safety. The PEAG is independent – it is not part of the government or the pharmaceutical industry.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

This report presents the MHRA's review of safety data for finasteride and expert advice on management of risks, as advised on by the PEAG. We have made changes to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in September 2023. The MHRA will continue to monitor the safety of finasteride closely and will issue further reports, if required, as further data become available. However, the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Finasteride

Finasteride, 5 mg formulation sometimes called Proscar, is used to manage benign (non-cancerous) prostatic hyperplasia (BPH). Finasteride, 1 mg formulation, sometimes called Propecia, is used to treat male pattern hair loss (MPHL). It belongs to a group of medicines called 5-alpha reductase inhibitors which block the conversion of testosterone to the androgen dihydrotestosterone (DHT) leading to a significant reduction in scalp and serum DHT. DHT is a hormone involved in the growth and repair of the prostate as well as the production of body hair. Finasteride is taken orally, with or without food as a film-coated tablet. It is available by prescription only and is not recommended for use in women or children. It is usually taken for a long time and if it is stopped, enlarged prostate symptoms or hair loss will usually come back. Finasteride 1 mg (Propecia) was first approved for use in MPHL in 1999 and finasteride 5 mg (Proscar) was first approved in 1992.

The prescription numbers for finasteride 5 mg are relatively stable at approximately 19,000-20,000 prescriptions per month. It is difficult to ascertain numbers of patients taking finasteride for MPHL as this medication is not prescribed on the NHS and is only available by private prescription. This means finasteride 1 mg is obtained from private hair loss clinics or more often, purchased from online pharmacies. The General Pharmaceutical Council (GPhC) set the standards for online pharmacies.

3.2 Reasons for the review

The MHRA previously completed a safety review into finasteride following concerns from patients regarding a lack of awareness of these side effects amongst patients and healthcare professionals. The MHRA issued a Drug Safety Update (DSU) in 2017 (Drug Safety (publishing.service.gov.uk)) regarding reports of depression and suicidal thoughts in men taking finasteride. Finasteride remains under continual monitoring by regulators and market authorisation holders (MAHs), and updates to the product information are implemented as required.

The current safety review of finasteride considered data from the published scientific literature, current product information, the NHS website, other international regulatory agencies and patients and the public. The focus of this review concerned the sexual and psychiatric side effects with finasteride and the potential of continuing side effects after stopping finasteride.

3.3 Warnings on sexual and psychiatric risks in the product information

Depression and finasteride

'Depression' has been closely monitored with finasteride since the approval of Propecia in 1999. In 2012, the term 'depressed mood' was added to the product information. Between 2014 and 2015, it was noted that for finasteride 1 mg (used to treat MPHL), there had been reports of 'depressive disorders' in the UK's Yellow Card database which may suggest a signal for the more serious reaction terms of depression and suicide. Considering the seriousness of the events, the product information for finasteride 1 mg and 5 mg was updated again in 2017 to include 'depression'. The patient information leaflet (PIL) was also updated to advise users that if they experience 'mood alterations such as depressed mood, depression and, less frequently, suicidal thoughts', they should stop taking their medicine and contact their doctor for further medical advice as soon as possible.

The MHRA published an article in its monthly 'Drug Safety Update' bulletin in May 2017 which highlighted there had been a number of reports suggesting a possible link to depression, and in rare cases, suicidal thoughts, with advice that patients should stop finasteride 1 mg (Propecia) immediately if they develop depression and inform a healthcare professional. The article also highlighted that the product information for finasteride 5 mg (Proscar) already lists depression as a possible adverse reaction.

Anxiety and finasteride

The product information for finasteride was updated to add 'anxiety' in 2017. The persistence of psychiatric side effects with finasteride has also remained under close monitoring.

Sexual side effects and finasteride

Sexual dysfunction (which includes decreased libido, erectile dysfunction, and decreased volume of ejaculate) was recognised at the time of licensing as being more frequently reported with finasteride than placebo in clinical trials, and 'ejaculation disorder' had also been reported in post-marketing use. These side effects have therefore been included in the product information since initial licensing of finasteride.

In 2010, the product information was updated to clarify that persistence of erectile dysfunction after stopping treatment had been reported in post-marketing use. In 2013, the product information was further updated to include 'decreased libido' and 'ejaculation disorder'.

Most recently, in 2019, the product information was updated to include ‘haematospermia’ (the presence of blood in the semen). Persistence of sexual side-effects has remained under close review by the MHRA.

3.4 Current product information

The possible side effects listed in the patient information leaflet for finasteride are:

- Depression (feeling of severe sadness and unworthiness)

Uncommon (may affect up to 1 in 100 people):

- you may be unable to have an erection (impotence)
- you may have less desire to have sex
- difficulty having an erection
- you may have problems with ejaculation for example decrease in the amount of semen released during sex. This decrease in the amount of semen does not appear to affect normal sexual function

Not known: frequency

- breast swelling or tenderness
- pain in the testicles
- blood in semen
- palpitations (feeling your heartbeat)
- persistent decrease in sex drive after discontinuation of treatment
- persistent problems with ejaculation after discontinuation of treatment
- male infertility and/or poor quality of semen
- changes in the way your liver is working, which can be shown by a blood test
- anxiety

Mood alterations and depression

Mood alterations such as depressed mood, depression and, less frequently, suicidal thoughts have been reported in patients treated with finasteride. If you experience any of these symptoms *(stop taking finasteride – 1 mg dose)* and contact your doctor for further medical advice as soon as possible.

3.5 Previous communications on risks with finasteride

The MHRA published an article in its monthly ‘Drug Safety Update’ bulletin in May 2017 which highlighted that there had been a number of spontaneous reports suggesting a possible link to depression, and in rare cases, suicidal thoughts, with advice that patients

should stop finasteride 1 mg (Propecia) immediately if they develop depression and inform a healthcare professional. The article also highlighted that product information for finasteride 5 mg (Proscar) already lists depression as a possible adverse reaction.

Who was involved in the review?

As part of the MHRA's safety review, many different organisations were consulted including the regulator of pharmacies the General Pharmaceutical Council (GPhC), National Institute of Clinical Excellence (NICE), General Medical Council (GMC), Royal Pharmaceutical Society (RPS), NHS website, Digital Clinical Excellence (DiCE), members of the PEAG, various charities, patients, and healthcare professionals.

Further information on the Pharmacovigilance EAG can be found here: Membership - Commission on Human Medicines - GOV.UK (www.gov.uk)

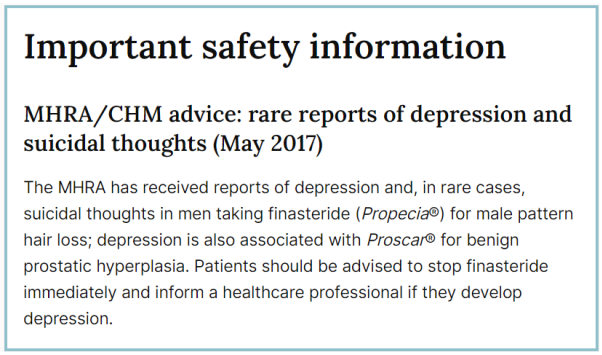
4. Current advice on sexual and psychiatric side effects

4.1 Information on depression and sexual side-effects provided in other sources of reference information for healthcare professionals

British National Formulary (BNF)

The BNF is an independent professional publication which provides prescribing information for healthcare professionals to support the safe, effective, and appropriate use of medicines. The BNF uses a variety of sources for its information, including the product information, literature, consensus guidelines, reference sources such as Martindale, and statutory information.

The following information is provided in the BNF in relation to finasteride:



Important safety information

MHRA/CHM advice: rare reports of depression and suicidal thoughts (May 2017)

The MHRA has received reports of depression and, in rare cases, suicidal thoughts in men taking finasteride (*Propecia*®) for male pattern hair loss; depression is also associated with *Proscar*® for benign prostatic hyperplasia. Patients should be advised to stop finasteride immediately and inform a healthcare professional if they develop depression.

Side effects:

- Common - sexual dysfunction
- Uncommon - breast abnormalities, skin reactions
- Frequency not known - angioedema, depression, infertility male, palpitations, testicular pain.

National Institute for Care and health Excellence (NICE) Clinical Knowledge Summary

NICE is a UK-based organisation that provides guidance and advice on health and social care.

What are the adverse effects of finasteride?

- Finasteride is generally well tolerated.

- Sexual dysfunction (decreased libido, erectile dysfunction, and ejaculation disorder) is common and tends to occur during the first year of treatment with finasteride. It decreases with the duration of treatment and usually resolves when treatment is discontinued. However, persistent sexual dysfunction after discontinued treatment has been reported rarely.
- Other adverse effects include:
    - Hypersensitivity reactions
    - Testicular pain
    - Haematospermia
    - Breast tenderness and enlargement
    - Mood alterations, including depressed mood, depression, and less frequently suicidal ideation have been reported in people treated with finasteride.
        - Monitor person for psychiatric symptoms.
        - Advise the person to stop finasteride immediately and inform a healthcare professional if they develop depression.

NHS website

Section 5. Side effects

Like all medicines, finasteride can cause side effects in some people, although not everyone gets them.

Common side effects

These common side effects happen in more than 1 in 100 people.

They usually improve after a while. However, talk to your doctor or pharmacist if these side effects bother you or do not go away:

- Problems getting an erection and less interest in having sex
- Problems with ejaculating, such as little or no semen

Serious side effects

Serious side effects are rare and happen in less than 1 in 1,000 people. Some people may notice these side effects after taking finasteride for a few months.

Speak to your doctor if you get:

- Any lumps, pain or swelling in your chest area or discharge from your nipples – these may be signs of a serious condition such as breast cancer
- Unusually low mood (depression) or thoughts of harming yourself

These are not all the side effects of finasteride. For a full list see the leaflet inside your medicines packet. You can report any suspected side effect to the UK safety scheme.

4.2 Stakeholder engagement and communications

The objective for meeting with these various stakeholders was to seek the views of patients about how the communication of side effects could be improved and identify potential risk minimisation measures. The MHRA also wanted to explore existing procedures and guidelines regarding the prescribing process of finasteride.

Patient groups

Post Finasteride Syndrome Network

Four members of the Post Finasteride Syndrome Network (PFSN) were invited to the meeting. Two had previous correspondence with the MHRA regarding side effects of finasteride. Members discussed their personal history with finasteride including persistent side effects, in particular depression and sexual dysfunction, even after cessation of the medication. They presented a short presentation on 'Post Finasteride Syndrome' and data from a survey of their members. The members specifically enquired if the MHRA could classify 'Post Finasteride Syndrome' as a recognised medical diagnosis, however this is not within the MHRA's remit. One of their objectives was to raise awareness of the potential side effects of finasteride and improvement in the communication of these side effects.

NHS website

The MHRA also met with the NHS website to discuss the layout of the website and subsequently the webpage was updated to include a link to the side effects at the top of the page.

4.3 Online prescribing of finasteride

The online prescribing of finasteride may be viewed as convenient for patients however, it does raise the issue of patients obtaining finasteride by a route which does not easily allow them to be monitored for psychiatric side effects, as outlined in the product information. The MHRA has therefore engaged with other organisations such as the General Pharmaceutical Council (GPhC), General Medical Council (GMC), online pharmacies and the Care Quality Commission (CQC) to raise awareness of some of the issues highlighted with the online prescribing of finasteride. We also engaged with Digital Clinical Excellence (DiCE) which aims to provide a collective clinical voice for digital healthcare providers. They have recently created 'Best Practice Guidelines for online pharmacies when prescribing finasteride *(*Best Practice Guidelines (digitalclinicalexcellence.com)*).*

5. Data for consideration

5.1 Literature review of finasteride and depression and suicidality, sexual dysfunction and 'post finasteride syndrome'

The MHRA performed a literature review using the following databases:

- Embase
- Embase Preprints
- MEDLINE
- Publicly Available Content

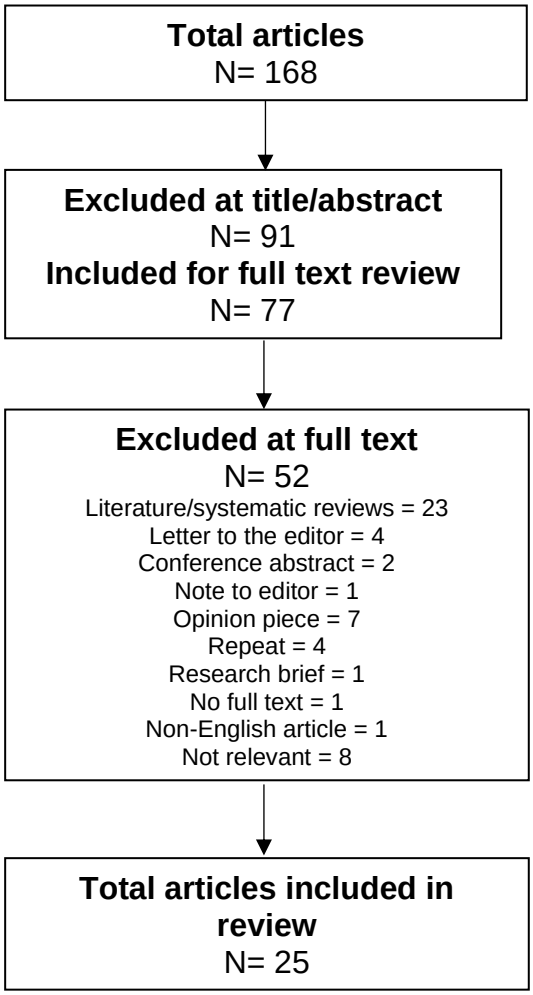
The databases were searched for publications dated from 1st January 2017 to 16th February 2023. This time period was chosen as the last significant regulatory action taken by the MHRA was an update to the product information to add 'depression' and a warning on the risk of suicidality, supported by an article in 'Drug Safety Update' in May 2017.

We included the following search criteria:

Drug substance: 'Finasteride 1mg', 'Finasteride 5mg', 'Propecia'

Safety concerns: 'psychiatric disorders', 'depression', 'suicidal ideation', 'suicide', 'Post Finasteride Syndrome', 'Self-harm', 'Sexual dysfunction', 'Ejaculation disorders'.

Figure 1: showing the search strategy



The titles and abstracts of the studies were screened, by MHRA assessors, of all 168 articles which were initially identified according to our search criteria (detailed above) and any disagreement was resolved through a third party. Full texts were retrieved from studies that satisfied all selection criteria. Reference lists of literature reviews were cross checked for any articles which satisfied the inclusion criteria.

Data was extracted from the 25 articles included in our review and populated into a pre-designed electronic data form to extract relevant information. The 25 articles were reviewed by two MHRA assessors, including an epidemiological assessor.

Sexual dysfunction

There were 13 articles focussing on the outcome of sexual dysfunction, of which 3 were meta-analyses and 10 were observational studies. Seven studies showed a significant increase rate of sexual dysfunction with finasteride. Of these studies, 3 were meta-analyses looking at randomised controlled trials (RCTs), however 2 of these looked only at the use of

5-alpha reductase inhibitors (5ARIs) in the treatment of BPH, a typically older population more likely to experience sexual dysfunction as compared to patients treated for male pattern hair loss (MPHL). The meta-analysis by Lee and others did specifically look at patients treated for MPHL and reported finasteride 1 mg had a relative risk of adverse sexual effects of 1.6 (95% CI 1.2 to 2.3) vs placebo, although in many included studies adverse events were self-reported and not evaluated using a validated tool.

The strength of the evidence from the observational studies included is subject to a number of methodological limitations. A few of the studies include patients drawn from clinics or from patient groups set up for finasteride side effects, this increases the likelihood of selection bias as patients who believe they are experiencing a drug related adverse event are more likely to volunteer for research. For several of the studies, the main endpoints are biological measurements relating to sexual dysfunction as opposed to investigating the presence of the sexual dysfunction. Many of the studies are also limited by small sample sizes reducing their power to accurately detect an association.

Two studies analysed data from the US FAERS database (Gupta and others and Baas and others), and both found an increase in reporting of adverse events with finasteride 1 mg as opposed to the 5 mg formulation. However, as these are based on spontaneous reports, they are subject to effects of stimulated reporting and reporter bias as well as uncertainties around causality.

Most of the studies showed the adverse effects occurred after the administration of finasteride, however some studies did not state or assess if the participant had pre-existing conditions. Kiguradze and others performed an observational study using electronic medical record data to assess whether duration of exposure affected adverse events. Their results showed that young men with more than 205 days of finasteride exposure had a 4.9-fold higher risk of persistent erectile dysfunction (p value <0.004) than men with a shorter exposure.

In addition to the presence of sexual dysfunction, some studies also looked at the persistence of these effects. One study did not show any evidence of persistent effects, 6 studies did show evidence of persistent sexual effects and 6 studies did not mention persistent effects. Of the 6 studies which showed evidence of persistent sexual effects, only 2 defined persistence as continued symptoms lasting for more than 90 days, or 3 months, after stopping finasteride.

Psychiatric dysfunction

There were 10 articles assessing the safety topic of psychiatric dysfunction, 2 were meta-analyses and 8 were observational studies. The total number of subjects included in the meta-analyses ranged from 199,454 to 265,672 and for the observational studies it ranged

from 34 to 2,236,876 subjects. In 7 of these studies, it was noted there were significantly higher rates of psychiatric adverse events with finasteride, with a hazard ratio (HR) ranging between 1.22 to 1.61. One meta-analysis (Deng and others) showed that in subgroup analyses, finasteride did not increase the risk of depression but dutasteride did (relative risk (RR) 1.53, 95% confidence interval (CI) 1.37 to 1.70, p <0.001). Dutasteride is another medication that inhibits 5-alpha reductase. Conversely, the systematic review and meta-analysis by Pompili and others concluded that finasteride is significantly associated with a risk of clinical depression, with the average risk of depression 1.31 times higher among subjects exposed to finasteride compared to subjects not exposed to finasteride (p <0.0001).

The strength of the evidence from the observational studies included is subject to a number of methodological limitations. A few of the studies include patients drawn from clinics or from patient groups set up for finasteride side effects, this increases the likelihood of selection bias as patients who believe they are experiencing a drug related adverse event are more likely to volunteer for research.

Five studies showed persistent psychiatric effects after discontinuation of finasteride, the remaining 5 studies either did not assess persistent adverse effects or did not mention this in their results. While most of these studies did not define persistence, 1 study defined it as continued symptoms for more than 3 months after stopping finasteride. One study used the subjects' own interpretation of persistent side effects.

All adverse events

There are inconsistent results within the included studies regarding psychiatric and sexual adverse effects with finasteride. Some of this inconsistency could be due to differences in methodologies between the studies, particularly in study outcomes and their assessment (for example, the use of different questionnaires to assess the side effects).

In general, the lower dose of finasteride 1 mg is associated with a higher risk of all side effects, compared to the 5 mg dose. Usually, the expectation would be an increase in the development and/or severity of symptoms with an increasing dose of drug. The exact reason for this difference is unknown, however we know that the patient population of men with MPHL are different to the population of patients using finasteride 5 mg for BPH.

There is biological plausibility for some of the sexual and psychiatric side effects of finasteride. Finasteride is a 5-alpha reductase inhibitor and reduces the levels of DHT in the body. By changing levels of this hormone, it is possible this leads to some of the sexual and psychiatric side effects reported. Pallotti and others performed a retrospective study in 55 subjects taking finasteride 1 mg for MPHL. Their data showed a decline in total sperm number even in andrologically healthy MPHL patients at 6 months compared with baseline. These changes were not statistically significant after 1 year and returned to baseline after

discontinuation. The small sample size and lack of control group are major limitations of this study.

There were 2 case series/reports and 2 from non-clinical laboratory studies. The results from the non-clinical studies were somewhat consistent with the clinical studies. However, there were identified limitations with the non-clinical studies which may affect the coherence. Most of the included studies did not state whether the removal of finasteride altered the frequency of the outcome.

The MHRA has sufficient evidence from the scientific literature to support the documented side effects of finasteride and the information already included in the product information. There is a signal for finasteride, depression, and suicidal ideation. This is also evidenced by patient testimonials. We have mixed evidence regarding the persistence of psychiatric and sexual side effects after stopping the medication. Many of the included studies suffer from limitations. The most consistent limitations include recall bias, selection bias, small sample size and concerns regarding methodology. This highlights the need for further larger prospective studies or larger observational studies with more detailed or appropriate methodology. However, adding the potential for persistence of psychiatric side effects to the product information is one of the issues that PRAC (Pharmacovigilance Risk Assessment Committee) has asked the MAHs to address in the next Periodic Safety Update Report (PSUR). Possible reasons for the inconsistency in the data are that many of the studies did not use validated tools for assessment of side effects, therefore direct comparisons could not be made.

The adverse effects of depression and sexual dysfunction are multifactorial, and it is important to note that there is a prevalence of these in the general population, so when looking at studies with no control group, this makes assessing the results difficult. One study by Kessler and others, found the global prevalence of erectile dysfunction using the IIEF questionnaire was between 13.1 to 71.2% and this questionnaire was used in many of the studies as a tool to evaluate sexual dysfunction. Another observational study by Capogosso and others published in 2013, included 114 men and found that erectile dysfunction affected 26% of men under the age of 40 years. This should be kept in mind when assessing causality.

Effect in different risk groups

Some studies included in the review, have found that those with a personal history of a psychiatric disorder or those who have a first degree relative with a psychiatric disorder, are more likely to develop side effects with finasteride. The same effect has also been shown for sexual dysfunction. However, many of these studies suffer from limitations, for example a small sample size and high risk of recall bias when using patient questionnaires and self-reporting symptoms. Nevertheless, nearly all the studies included the recommendation that

patients should be screened for underlying risks and monitored for side effects regardless of their clinical or family history.

Effect of dose (1 mg vs 5 mg)

Some studies have shown a similar side effect profile for both finasteride 1 mg and 5 mg dose, while others have suggested a higher risk of all side effects in men using finasteride for hair loss (1 mg dose). The authors attributed this to a different patient profile which may contribute to their symptoms or likelihood of suffering side effects. It is well known that the subjects who use finasteride 1 mg for hair loss differ from the patients who use finasteride 5 mg for BPH. The former usually are young men using finasteride for hair loss. For some of these men, hair loss may be the cause, or lead to depressive symptoms. The product information for finasteride 1 mg and 5 mg are similar, with depression and persistent sexual side effects listed for both. Rash, pruritus and urticaria is additionally listed for the 5 mg dose. It is worth noting that usage of the 5 mg dose is higher (from data presented in the PSUR) than the 1 mg dose, however the reporting of side effects is seen more with the 1 mg dose. This also correlates with data from the Yellow Card database, which is explained in more detail in section 5.2.

Persistent side effects

The current product information states that in '*some cases persistence of sexual ADRs may occur after discontinuation of treatment*' therefore the data presented confirm what is already listed. However, this does not take into account the persistence of psychiatric ADRs which is currently not included in the product information.

Data from the literature review regarding the persistence of side effects was inconclusive. Some studies did show a proportion of patients with persistent sexual and psychiatric symptoms after stopping finasteride, however some studies did not. The persistence of psychiatric side effects has been reviewed in previous PSURs (from 2015 to 2019) however it was concluded that cases contained insufficient clinical information to allow for causality assessment. It was noted that several times more cases reported with finasteride 1 mg than with finasteride 5 mg, despite considerably higher exposure to the latter.

Full details of the systematic review and complete summary of the evidence are available upon request.

5.2 Yellow Card data

The Yellow Card database was searched by an MHRA assessor using the MedDRA (version 25.1). MedDRA is a medical terminology dictionary used by regulators. Two searches were performed, the first identified reports of finasteride reported alongside the Higher-Level Group Term (HLGT) of 'Sexual dysfunction and fertility disorders' and the second identified

reports of finasteride reported alongside the HLGTs of ‘Depressed mood disorders and disturbances and suicidal and self-injurious behaviours’. The database was searched up to and including 5th January 2023.

There were 196 Adverse Drug Reaction (ADR) reports (out of a total of 606 reports, 32%) where patients reported both sexual dysfunction and depressive disorders. There has been a suggestion in previous data that these two conditions are linked, and it is widely known that one condition could be a cause, or at least related, to the other condition.

Fatal ADRs

There were 4 fatal adverse drug reactions (ADRs) listed as ‘completed suicide’ who were all male and between the ages of 21 to 30 years old. No information on age was provided for some of the reports. The ADRs were received between 2015 to 2019.

Time to onset of symptoms

Across both sexual dysfunction and depressive disorders, time to onset of symptoms was documented in 252 reports (42% of total reports). The average time to onset was 330 days (around 10.8 months) and the range was from 1 day to 5,923 days. The average time to onset for depressive symptoms was 364 days and for sexual dysfunction this was 306 days.

Sexual dysfunction

The MHRA has received a total of 375 Yellow Card reports from 27th November 1992 until 5th January 2023 of finasteride and Sexual dysfunction and fertility disorders. There were 369 reports in males, 6 were of unknown sex and there were no reports in females. The age range of reports was from 18 to 81 years. The outcome was recorded as ‘not recovered/not resolved’ in 188 reports (around 50%). Two hundred and twenty-six of these reports related to the 1 mg dose of finasteride and/or the indication for alopecia. One hundred and ten reports related to the 5 mg dose and/or indication for BPH. Thirty-nine reports were for an unknown dose and/or indication. The top 3 ADR terms for finasteride 1 mg were: erectile dysfunction, decreased libido, and depression. The top 3 ADR terms for finasteride 5 mg were: erectile dysfunction, decreased libido, and ejaculation disorder.

Depressive disorders

There was a total of 231 reports of finasteride and Depressed mood disorders and disturbances or Suicidal and self-injurious behaviours from 2nd February 1993 until 5th January 2023. 222 were in males, 4 in females and in 5 reports the sex was unknown. The age range was from 15 to 89 years. The outcome was recorded as ‘not recovered/not resolved’ in 90 reports (around 39%). The average time to onset for the reaction was 281 days. In 10 reports, patients were on anti-depressants or anti-anxiety medication, however

there is no information on when the medication was started (pre or post finasteride). One hundred and fifty-five reports related to the 1 mg dose and/or indication for alopecia. Fifty reports related to the 5 mg dose and/or indication for benign prostatic hyperplasia. Twenty-six reports were for an unknown dose and/or indication. The top 3 ADR terms for finasteride 1 mg were: depression, loss of libido, and suicidal ideation. The top 3 ADR terms for finasteride 5 mg were: depression, suicidal ideation, and anxiety/stress.

Yellow Card data conclusion

The most common side effects reported for both doses of finasteride were depression, loss of libido, suicidal ideation, stress/anxiety, erectile dysfunction, and ejaculation disorder. These terms are all listed in the current product information. There are more reports per ADR term for finasteride 1 mg, compared with finasteride 5 mg. For example, for the term insomnia there were 44 reports relating to the 1 mg dose but only 3 reports for the 5 mg dose. For muscle atrophy/asthenia there were 28 reports relating to the 1 mg dose but only 2 reports for the 5 mg dose. This is true even when taking into account the higher number of total reports included for the 1 mg dose (226 reports vs 110 reports and 155 vs 50 for sexual dysfunction and depressive disorders respectively). It should be clarified that even though there are a different number of reports for the 1 mg and 5 mg doses, this does not necessarily mean a different level of risk.

In nearly a third of reports (32%) patients reported both sexual dysfunction and depressive disorders suggesting there is an overlap of these symptoms.

The MHRA has 4 fatal reports with finasteride, all in men between the ages of 21 to 30 years old.

The range of time to onset of symptoms was large, 1 day to 5,923 days with an average of 330 days. This information was only documented in 42% of reports.

Given the inherent limitations such as under reporting and lack of denominator of spontaneous reporting schemes, it is not possible to draw any firm conclusions from the trends seen with the spontaneously reported data in the UK. The scale of the persistence of ADRs is also difficult to gauge as there may be a reluctance to report these types of events when they occur, and it is difficult to be certain of the level of usage because accurate private prescribing data is not available.

5.3 Actions taken by other international regulators

Other international regulators such as The French Agence nationale de sécurité du médicament et des produits de santé (ANSM), Health Canada, United States Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) have

also completed, or are undergoing, safety reviews of finasteride. The ANSM announced that they will require MAHs to include additional labelling on boxes to point patients to read ANSM-online information on the risks of psychiatric and sexual ADRs. Health Canada have updated the Canadian product monographs (CPMs) of finasteride to include the risk of suicidal ideation. In June 2022, the FDA also updated the patient labelling for finasteride to include suicidal ideation, sexual dysfunction and psychoneurocognitive adverse events. Recently, the PMDA have also updated their product information to include precautions concerning suicide-related events.

5.4 Survey results from the Post Finasteride Syndrome (PFS) Network questionnaire

The PFS network is a registered charity that works with researchers to help further understanding of Post-Finasteride Syndrome and identify potential targeted therapeutic treatments.

The PFS network completed a survey which was sent to their members and included a multi-part questionnaire. They received 427 submissions and provided their preliminary results from the ongoing data analysis of this survey. The most pertinent points form the survey are that just over half of respondents used finasteride for 200 days or less and report a large variety of symptoms including several physical symptoms which are not included in the product information as known side effects for example, muscle cramps/twitching, thin skin, fatigue, and muscle weakness.

6. Discussion

In this safety review of finasteride, the MHRA have analysed data from internal signals, the Yellow Card database, scientific literature, patient questionnaires, stakeholder engagement sessions and regulatory action taken in other countries.

The literature review showed mixed outcomes from studies with regards to finasteride, suicide, depression, and sexual dysfunction. It is clear, when looking at pharmacovigilance databases, there are increased signals for these side effects, however there may be other possible reasons contributing to these signals including an increase in media attention and the possible 'nocebo' effect. Depression is multifactorial and could be due to underlying psychiatric disorders, the medication itself, related to the sexual side effects of finasteride and/or the condition it is used to treat (BPH and hair loss).

Previous safety reviews have investigated these adverse effects, with no additional risk minimisation measures recommended, although the product information has been updated to include these adverse effects. Nonetheless, patients have disclosed their experiences with us and the devastating effects this can have on their quality of life. A common theme from the conclusions in the literature review, was that healthcare professionals should be explaining potential side effects clearly, completing pre-screening questionnaires to identify patients at risk of adverse effects, and actively monitoring patients.

Another important aspect of this review concerns the prescribing process for finasteride 1 mg, which is through private hair loss clinics or more commonly, purchased online. The MHRA met with online pharmacies, and while some do have thorough screening and monitoring processes in place, others do not. However, the regulation of pharmacies, including online pharmacies, is not within the remit of the MHRA.

Most of the side effects that were attributed to finasteride in the published studies and Yellow Card data, are already in the product information, including the patient information leaflet. However, it was identified that there is scope for additional risk minimisation measures to address patient concerns around lack of awareness of these side effects and the persistence of sexual dysfunction in some patients after stopping treatment.

Advice on next steps was sought from the Pharmacovigilance Expert Advisory Group (PEAG). The PEAG recommended the introduction of a patient card inside the box to highlight some of the psychiatric and sexual side effects. The PEAG also advised that a Drug Safety Update (DSU) article would be beneficial to highlight the potential for sexual dysfunction to persist following the end of treatment, to inform healthcare professionals of the introduction of the patient card and to reinforce that patients should be actively monitored while on finasteride for any adverse events. It was also suggested to add 'suicidal ideation'

to section 4.8 of the SmPC and PIL. The PEAG also supported continued work with other organisations regarding online prescribing of finasteride and to increase awareness of the potential side effects among healthcare professionals.

7. Conclusion

In conclusion, the MHRA have further reviewed the safety of finasteride with a focus on the sexual and psychiatric side effects. The MHRA assessed evidence in the scientific literature, product information, from other international regulatory agencies and from the patients and the public.

Actions taken include updates to the product information to include ‘suicidal ideation’ in section 4.8 of the SmPC and to the PIL. The views of patients have been sought on the wording for the patient card which should be introduced over the next 9-12 months. A copy of these cards can be found in annex 1. We have issued a Drug Safety Update (Finasteride: reminder of the risk psychiatric side effects and of sexual side effects (which may persist after discontinuation of treatment) - GOV.UK (www.gov.uk)) which will include information on the additional risk minimisation measure of the patient cards and highlight the potential for the persistence of sexual side effects after discontinuation of the medication. We have engaged with other organisations to raise awareness of some of the issues with online prescribing of finasteride. In addition, DiCE have produced a ‘Best Practice Guideline’ for male pattern hair loss Best Practice Guidelines (digitalclinicalexcellence.com). This is aimed at HCPs and ‘aims to reduce unwarranted variation, help mitigate adverse effects of treatment and distinguish the properly licenced and regulated services from those unqualified and potentially dangerous sources online’.

The MHRA continues monitoring the effectiveness of the measures and generally of adverse drug reactions reported and takes further action as needed.

If you are a patient on finasteride, please discuss any concerns you have with your healthcare professional.

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9. Glossary of terms

Adverse drug reaction (ADR)
A response to a medicinal product which is noxious and unintended where a causal relationship between the medicinal product and adverse event either known or strongly suspected.

Agence nationale de sécurité du médicament et des produits de santé (ANSM)
Responsible for assessing the benefits and risks associated with the use drugs and other medical products throughout their life cycle in France.

Bias
Disproportionate weight in favour of or against an idea or thing.

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy, and quality of medicinal products.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Contra-indicated/Contraindication
When a drug should not be used in a specific situation, condition, or group of people because it may be harmful to the person.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Food and Drug Administration (FDA)
Federal agency responsible for regulating and overseeing the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food, cosmetics, products that emit radiation and tobacco products in the USA.

FDA Adverse Event Reporting System (FAERS database)
Database of adverse event reports for all marketed drug and therapeutic products in the US.

Good Laboratory Practice
A set of rules and criteria intended to assure the quality and integrity of non-clinical laboratory studies.

Hazard ratio
Statistical measure used in medicine and research. It compares the chance of an event occurring in one group to that of another at a particular time or over a subset of a study's time.

Health Canada
Department of the Government of Canada responsible for national health policy.

Healthcare databases
Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient's care.

Incidence
The occurrence of new cases of a disease or condition in a population over a specified time period.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK.

Meta-analysis
A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Nocebo effect
When negative expectations of the patient regarding a treatment cause the treatment to have a more negative effect that it otherwise might have.

Non-clinical or pre-clinical studies
In drug development, preclinical development, also named preclinical studies and non-clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected.

Observational study
Research process where individuals or organisations examine something without manipulating or intervening in it.

Patient Information Leaflet
Medicine packs includes a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SmPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Pharmacovigilance Risk Assessment Committee (PRAC)
Committee that assesses and monitors the safety of human medicines in Europe.

Pharmaceutical and Medical Devices Agency (PMDA)
Independent administrative institution responsible for ensuring the safety, efficacy and quality or pharmaceuticals and medical devices in Japan.

Placebo
Substance or treatment which is designed to have no therapeutic value.

Periodic safety update report (PSUR)
These are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation.

Randomised controlled trial (RCT)
A type of study design that involves randomly assigning participants to either an experimental group or a control group to measure the effectiveness of an intervention or treatment.

Retrospective study
A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Risk Ratio/Relative Risk
A risk ratio (RR), also called relative risk, compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group.

Stakeholder
Any person, group of people or other organisation that has an interest in the activities of a business or organisation.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Systematic review
A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Vigibase
Unique WHO global database of reported potential side effects of medicinal products.

10. Annexes

Annex 1

Patient card for finasteride 1mg:

This medication can cause side effects including **depression.** In some cases, it may lead to having **thoughts of suicide.** If you experience these symptoms, stop taking Finasteride and contact your doctor for further medical advice as soon as possible.

Decreased sex drive and **erectile dysfunction** have also been reported (which in some cases continued after treatment was stopped).

If you experience any side effects, including those not listed in the leaflet, speak to your doctor or pharmacist or report directly to the Yellow Card scheme

Patient card for finasteride **5mg:**

This medication can cause side effects including **depression.** In some cases, it may lead to having **thoughts of suicide.** If you experience these symptoms, contact your doctor for further medical advice as soon as possible.

Decreased sex drive and **erectile dysfunction** have also been reported (which in some cases continued after treatment was stopped).

If you experience any side effects, including those not listed in the leaflet, speak to your doctor or pharmacist or report directly to the Yellow Card scheme (www.mhra.gov.uk/yellowcard).