MHRA PUBLIC ASSESSMENT REPORT

The risk of male breast cancer with finasteride

December 2009

PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices 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. In our public assessment reports, we discuss the evidence for a safety issue associated with a particular drug or drug class. This report discusses our review of the risk of male breast cancer associated with medicines containing finasteride.

5 mg finasteride tablets have been licensed under the brand name Proscar in the UK since 1992, as a treatment for benign prostatic hyperplasia (BPH)[a] in men. 1 mg finasteride tablets have been licensed in the UK since 1999 under the brand name Propecia, and are used to treat men with androgenetic alopecia[b].

As with any medicine, the use of finasteride may lead to suspected adverse drug reactions[c] (ADRs) in some individuals. Adverse reactions that are recognised to occur in association with a medicine are listed in the information accompanying the medicine[d]. Although male breast cancer is not currently listed as an ADR in the product information for finasteride, an association between finasteride and male breast cancer has been suggested from individual case reports[e], and data presented in the medical literature. To assess this risk, a review of the evidence was undertaken, which included data from clinical trials, cases of ADRs reported with finasteride use and a discussion of the mechanism of action of finasteride. The data were initially considered by UK expert committees (the Commission on Human Medicines[f] and their expert advisory group [the Pharmacovigilance Expert Advisory Group[g]]) and also reviewed by the European Pharmacovigilance Working Party[h].

Results

Fifty cases of male breast cancer have been reported worldwide with the use of 5 mg finasteride (Proscar) and three cases have been reported with the use of 1 mg finasteride (Propecia). Most cases reported with Proscar use occurred within 5 years of starting treatment. Although the overall incidence of male breast cancer in clinical trials in patients who received 5 mg finasteride was not significantly different compared to patients who did not receive finasteride (7·8 per 100 000 patient-years[i] vs 3·8 per 100 000 patient-years; p=0.328), the data from these trials showed that there was a trend towards male breast cancer occurring more frequently in patients who had received finasteride, than in those who did not.

Conclusions

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[a] Enlargement of the prostate gland, which causes difficulty in urinating

[b] Male pattern hair loss

[c] A response to a drug that is unintended, and harmful or unpleasant

[d] See the Electronic Medicines Compendium (product information) website

[e] Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our Yellow Card Scheme (www.yellowcard.gov.uk)

[f] An independent body which gives advice to UK government Ministers on the safety, quality and efficacy of medicines

[g] A group of medical and scientific experts on pharmacovigilance who advise on, and support, the work of the Commission on Human Medicines

[h] A group who provide recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

[i] The number of patients in a study multiplied by the number of years that these patients were followed

Cases of male breast cancer have been reported for finasteride, and the review suggested that an increased risk of male breast cancer associated with finasteride use cannot be excluded. Patients using finasteride products should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain or nipple discharge because these may be signs of a serious condition, such as breast cancer.

On the basis of the review, it was recommended that a warning on the risk of breast cancer should be included in the product information for all medicines containing finasteride.

Outcome
The following warnings on the risk of male breast cancer will be included in the Summaries of Product Characteristics (SPCs) and patient information leaflets (PIL) for the finasteride products Proscar and Propecia:

Proscar SPC wording:

Section 4.4 Special warnings and precautions for use
Breast cancer in men
Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and in the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Section 4.8 Undesirable Effects
In addition, the following has been reported in clinical trials and post-marketing use; male breast cancer (see 4.4 Special warnings and precautions for use).

Propecia SPC wording:

Section 4.4 Special warnings and precautions for use
Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period.
Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Section 4.8 Undesirable Effects
In addition, the following have been reported in postmarketing use: persistence of erectile dysfunction after discontinuation of treatment with PROPECIA; male breast cancer (see 4.4 Special warnings and precautions for use).

Proscar and Propecia PIL wording:

Possible side effects
You should promptly report to your doctor any changes in your breast tissue such as lumps, pain or nipple discharge as these may be signs of a serious condition, such as breast cancer.

1. INTRODUCTION

(See glossary for explanation of terms used in this document)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices 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. In our public assessment reports, we discuss the evidence for a safety issue associated with a particular drug or drug class. This report discusses our review of the risk of male breast cancer associated with finasteride.

In the UK, 5 mg finasteride (Proscar) is indicated for the treatment of benign prostatic hyperplasia (BPH). Finasteride is also licensed at 1 mg (Propecia) to treat androgenetic alopecia in men.

Although the safety of finasteride has remained under close review by the MHRA since 1998, there has been an increasing number of case reports received by the MHRA of male breast cancer associated with finasteride products. This prompted a review of the evidence on the risk of male breast cancer with finasteride use. The following report summarises the evidence and conclusions from the review, which included data from clinical trials, reports of adverse drug reactions (ADRs) received after licensing[a], a Prescription Event Monitoring (PEM) study[b], and data from the scientific literature. The review also considered whether there was a plausible biological mechanism for male breast cancer to occur with finasteride use, which is summarised at the end of this report.

[a] Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our Yellow Card Scheme (www.yellowcard.gov.uk)

[b] A study that monitors the safety of newly licensed medicines using questionnaires completed by general practitioners

2. BACKGROUND

2.1. Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a non-cancerous enlargement of the prostate, associated with lower urinary tract symptoms (LUTS) such as difficulties in passing urine, urinary retention and poor urinary flow.

The causes of BPH are largely unknown; however enlargement of the prostate is a normal consequence of the aging process. Prostatic enlargement is found in approximately half of all men aged 51–60 years (Berry *et al.*, 1984), and changes in the prostate suggestive of BPH have been found in up to 70% of men aged 60–70 years (Lynch *et al*., 1991). Risk factors aside from increasing age include androgen levels, familial history and patient ethnic origin.

The diagnosis of BPH can involve the use of non-invasive techniques such as measurement of peak urinary flow rates (Qmax) and digital examination of the prostate. Treatment options available include surgical intervention or drug therapy. In the UK, two drug classes are licensed for the treatment of BPH: alpha-adrenoceptor antagonists (alpha-blockers; currently the preferred first-line therapy for men with moderate to severe LUTS) and the 5α-reductase inhibitors 5 mg finasteride (Proscar; see section 2.3) and dutasteride.

2.2 Androgenetic alopecia

Androgenetic alopecia is a common condition characterised by a defined pattern of progressive hair loss. It affects both men and women although the incidence is greatest in men. The prevalence is high with approximately 50% men of white ethnic origin affected by age 50 years (Hamilton, 1951).

Determining factors for androgenetic alopecia include genetic predisposition and circulating androgen levels. Although there are no physical symptoms resulting from androgenetic alopecia, it is a stressful condition that can cause psychological symptoms including depression.

Treatments available include the drug therapies minoxidil and finasteride. Finasteride is administered orally in a 1 mg dose form for androgenetic alopecia (Propecia; see section 2.3).

2.3 Finasteride products (Proscar and Propecia)

Finasteride is a competitive and specific inhibitor of human type II 5α-reductase, an intracellular enzyme that metabolises testosterone into the more potent androgen dihydrotestosterone (DHT) in target tissues. Inhibition of this enzyme with finasteride results in significant and rapid decreases in serum and tissue DHT concentrations, with significant suppression of DHT reached within 24 hours of dosing. Finasteride inhibits DHT-mediated effects on target tissues without lowering serum testosterone, or affecting testosterone-mediated effects in tissues.

The two licensed drugs in the UK which contain finasteride are Proscar (licensed in the UK in 1992 and available as a prescription-only medicine [POM]) and Propecia (licensed in the UK in 1999 and also only available by prescription).

Proscar is used for the treatment and control of BPH, to reduce the enlargement of the prostate, improve urinary flow and improve the associated symptoms in men. Proscar is given orally at a dose of 5 mg daily. In BPH, the enlargement of the prostate gland depends upon the conversion of testosterone to DHT within the prostate. Proscar is highly effective at lowering circulating and intraprostatic DHT and reducing both the incidence of acute urinary retention and the need for surgery, including transurethral resection of the prostate and prostatectomy.
Propecia is used for the treatment of men with androgenetic alopecia to increase hair growth and prevent further hair loss. Propecia is given orally at a dose of 1 mg daily. Hair follicles contain type II 5α-reductase; men with a genetic deficiency of type II 5α-reductase do not experience male pattern hair loss (Zhu *et al*., 1998). In men with androgenetic alopecia, the scalp contains miniaturised hair follicles and increased amounts of DHT. Propecia decreases scalp and serum DHT concentrations, and also inhibits a process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process. During 2008 in the UK, the use of 5 mg finasteride for the treatment of BPH was approximately 17 times greater than the use of 1 mg finasteride to treat androgenetic alopecia. Compared to the other BPH treatments, finasteride is the second-most used treatment licensed for BPH following tamsulosin, an alpha-blocker[a].

2.4 Breast cancer

Male breast cancer is a rare disease with an annual incidence in Europe of one case in 100 000 man-years (Sasco *et al*., 1993). There are distinct differences between male and female breast cancer; overall, the risk of breast cancer in males is one-hundredth the risk of breast cancer in females (Sandler *et al.*, 1994) and male breast cancer progresses in a similar way to breast cancer in postmenopausal women. Less than 1% of all breast cancer patients are male (Sasco *et al.*, 1993; Borgen *et al.*, 1992), including cases in the UK[b] and because of the rarity of the disease, little is known of the causes of male breast cancer in comparison to female breast cancer. The consequence of this rarity is that male breast cancer has been understudied, and the existing small sample size limits the epidemiological methodology available to study this disease. However, overall the incidence of male breast cancer is increasing worldwide, especially in developing countries (Contractor *et al*., 2008). In the USA between 1973 and 1998 the incidence of male breast cancer increased from 0·86 to 1·08 per 100 000 men (Giordano *et al*., 2004).

In comparison to female breast cancer which has a bimodal age-frequency distribution with peaks at 52 years and 71 years, male breast cancer has a singular peak in age-frequency distribution at 71 years (Anderson *et al*., 2004). Its pathology and treatment are similar to female breast cancer. The clinical manifestations of male breast cancer include: breast mass (seen in 75% of patients), nipple retraction (9%), nipple discharge (6%), skin/nipple ulceration (6%) and Paget's disease of the nipple (1%) (Jepson & Fentiman, 1998). Surgical treatment is the preference for localised tumours, together with possible adjuvant hormonal therapy, chemotherapy or radiotherapy. Hormones are believed to play a significant role in the development of breast cancer; for breast cancer that is oestrogen-receptor-positive, hormonal manipulation is aimed at reducing the

[a] Data derived from IMS Health Midas database 01/10/2007 – 30/09/2008
[b] From Cancer Research UK: http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/index.htm

binding of the hormone oestradiol to the oestrogen receptor. This is accomplished either by using the antioestrogen tamoxifen to block oestradiol binding to the oestrogen receptor, or by using selective aromatase inhibitors such as anastrozole to reduce the amount of oestradiol present in the breast cancer cells. Oestradiol is the main oestrogen in humans, and oestrogen in men is normally obtained via the conversion of T to oestradiol and the peripheral conversion of androstenedione to oestrone in fat cells (Siiteri & MacDonald, 1973).

The survival rate for men with breast cancer is lower than for women with the same disease, because of their increased age at diagnosis and more advanced stage of the disease at presentation (Erhan *et al*., 2006), and because of the rarity and hence lack of awareness of the disease among men. No differences in outcome between the sexes are found when male and female age-matched and stage-matched breast cancers are compared (Willsher *et al.*, 1997).

Risk factors associated with male breast cancer include genetic and epidemiological factors. Major genetic factors include mutations in the BRCA gene family; in women, mutations of the BRCA1 and BRCA2 tumour suppressor genes are associated with a breast cancer risk of 50–80%[a]. BRCA2 gene mutations in men have a risk of 5–10% and BRCA1 mutations may increase the lifetime risk of breast cancer in men to about 1%. A positive family history is also a risk factor; several population based studies have shown that approximately 20% of cases of male breast cancer had a history of breast cancer in a female relative (Ewertz *et al*., 2001; Johnson *et al*., 2002). Genetic disorders such as Klinefelter's syndrome are further risk factors for breast cancer in men. Epidemiological factors include conditions affecting oestrogen/testosterone hormone balances such as testicular disorders, obesity and radiation exposure; prostate cancer; prostate cancer treatment; and gynaecomastia . Numerous studies have investigated a possible link between breast cancer and gynaecomastia, with some studies showing no evidence of increased incidence of gynaecomastia in mastectomy specimens from male breast cancer cases (Fentiman *et al.*, 2006) and other studies identifying an association between the two (Weiss *et al*., 2005).

[a] http://www.cancerhelp.org.uk/type/breast-cancer/about/risks/breast-cancer-genes (Accessed 17/11/09)

3. SUMMARY OF DATA

3.1 Case reports of ADR data

3.1.1 UK cases of male breast cancer with finasteride reported to the MHRA

In total there have been five UK case reports to the MHRA of male breast cancer associated with finasteride 5 mg (all indicated for BPH). The ADR profiles of finasteride and other drugs indicated for BPH and alopecia were compared.

Gynaecomastia was the most common ADR in the *Reproductive and Breast Disorders* System Organ Class (SOC)[a], and is a known side effect of finasteride. The total number of gynaecomastia cases for finasteride was 75 (69 cases with 5 mg dose; four cases with 1 mg dose; two cases where the finasteride dose was unknown). Tamsulosin had the second highest number of cases (11).

Finasteride was associated with the highest number of ADRs in each breast cancer-related SOC compared to other drug substances indicated for BPH, even though it does not have the greatest usage in the UK (section 2.3). Tamsulosin is associated with the second highest number of ADRs and it has the greatest usage in the UK for BPH, followed by finasteride, alfuzosin, doxazosin, dutasteride, indoramin, terazosin and prazosin.

A statistical estimate of relative reporting rates is given by a measure called the Empiric Bayes Geometric Mean (EBGM)[b]. The EBGM of 29.7 (EB05 6.1; EB95 67.5) for male breast cancer associated with finasteride use from MHRA data was classed as a signal[c].

To date, there have been no reported cases of male breast cancer associated with 1 mg finasteride use in the UK. The total number of ADRs in the *Reproductive and Breast Disorders* SOC for finasteride (both doses) was 119; seven ADRs in this category were reported for minoxidil.

Overall, there were fewer ADRs associated with the 1 mg dose of finasteride compared with the 5 mg dose. This is to be expected as UK usage is much lower for the 1 mg dose. In addition, ADRs can be dose-dependent—the higher the dose the greater the risk of experiencing an adverse reaction. However, finasteride at the 1 mg dose was associated with four cases of changes in blood testosterone levels.

3.1.2 Worldwide case reports of breast cancer with finasteride (held on marketing authorisation holder[d] database)

There were 50 worldwide case reports of male breast cancer in patients aged between 54–88 years (mean age 71 years) treated with 5 mg finasteride (Proscar), which were received between April 1992–November 2009 These included 44 medically confirmed reports.

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[a] An ADR can be grouped or categorised according to the body system or organ it affects – known as the System Organ Class (SOC)

[b] The size of the EBGM may give some idea about the strength of evidence from case reports for a particular reaction; ie, the larger the value, the stronger the potential association between the drug and the reaction. More than three reports of a reaction, with an EBGM≥2·5 and an EB05≥1·8, is classed as a signal. EB05 and EB95 are the lower and upper bounds of the 2-sided 90% confidence intervals around the EBGM.

[c] An indicator or reported information suggesting that a drug may be associated with a previously unrecognised ADR or an existing ADR that is different from current expectations

[d] The company that hold the licence of a particular medicine and are responsible for that medicine

Temporal relationships are considered to be important factors when considering the causal association for these cases. The time to onset could be estimated in 35 of the reports, with a mean time to onset of approximately 44·4 months (the median time to onset was 36 months (range: 5 weeks to 11 years). Twenty-seven cases occurred after finasteride treatment for a minimum of 1 year.

In eight cases, patients were diagnosed with breast cancer within a year after starting therapy. Twenty-seven of the cases occurred at least 1 year after starting finasteride therapy. Specifically: four cases occurred within 1–2 years, six cases within 2–3 years, five cases within 3–4 years, three cases within 4–5 years and nine cases occurred after at least 5 years. The time to onset in 14 cases was unknown and nine cases occurred less than 1 year after starting finasteride therapy. In seven of the 35 reports, therapy with finasteride was discontinued (7–24 months) before breast cancer was diagnosed, whereas in eight reports, finasteride therapy was continued after the diagnosis of breast cancer.

Three medically-confirmed cases of male breast cancer in patients treated with finasteride (Propecia) were reported between September1997–November 2009; two cases with the 1 mg dose, and one where the dose was unknown. The relatively short times to onset in these cases makes a causal association with finasteride unlikely, although finasteride may have played a contributory role with other underlying factors. It is important to recognise that underreporting of ADRs is a recognised limitation of all ADR-reporting schemes (Rawlins *et al.*, 1992; Meyboom *et al.*, 1997).

Although finasteride is not indicated for use in women, four cases of breast cancer with 'off-label' use of finasteride in females were received in the US, one with Proscar and three with Propecia. The times to onset in the female breast cancer cases were 6 months, 9–10 months, and 1 year (one case unknown), which are quite short periods of exposure. While there may be some unknown contributory factors, the difference in endogenous hormone levels between men and women, in particular for oestrogen, may mean that a lower dose of finasteride over a shorter period of time in women may be equivalent to a higher dose of finasteride over a longer time period in men to reach similar levels of risk for breast cancer.

3.2 Preclinical data

High doses of finasteride in life-long rodent studies showed no evidence of carcinogenic potential. There is no evidence from preclinical studies that finasteride treatment is causally associated with breast cancer development.

3.3 Clinical data

3.3.1 Hormonal changes during treatment with finasteride

Hormone levels were measured in many finasteride studies with consistent results.

The PROSCAR Long-Term Efficacy and Safety Study (PLESS) examined 3040 men with moderate to severe symptoms of BPH who were equally randomised to 5 mg finasteride daily or placebo and treated for up to 4 years (McConnell *et al.*, 1998). In this study, approximately 10% of the patients at each centre were randomly selected to have their dihydrotestosterone (DHT), testosterone (T), and luteinising hormone (LH) levels

measured at baseline and yearly thereafter. Of these, 4-year data were available for 118 finasteride-treated and 111 placebo-treated patients.

Daily 5 mg finasteride treatment for up to 4 years reduced serum DHT by approximately 70%. This was accompanied by a corresponding 10–20% increase in serum testosterone levels, which remained within the physiological range. Similarly, a 13% increase in serum testosterone levels which remained within the physiological range was observed in the phase III programme for 1 mg finasteride. This was expected as finasteride lowers serum DHT by inhibiting type II 5α-reductase and leads to an anticipated small increase in serum T due to a decrease in the metabolism of T to DHT.

In PLESS an increase of about 10% in LH levels was detected in finasteride-treated patients, which was within the physiological range and was consistent with results of previous studies (Gormley et al, 1992; The Finasteride Study Group, 1993). In a separate phase I study, no difference in FSH levels was observed between men treated with finasteride or placebo over an 11-day period (Gormley et al, 1990). Likewise in the Phase III programme for 1 mg finasteride, no effects on serum LH or FSH were observed relative to placebo.

Data from studies of 5 mg finasteride daily showed no significant change in serum oestradiol after 6 months of treatment; however, the assay used to measure oestradiol may not have been very sensitive, and the sensitivity has greatly improved since this study. Although oestradiol measurements using a more sensitive assay do not exist for 5 mg finasteride, the Propecia Safety Study compared serum oestradiol levels measured with a sensitive assay in patients given either 1 mg finasteride or placebo. The median percent increase from baseline in serum oestradiol was significantly higher in the finasteride group (n=69) (p=0.027) compared with the placebo group (n=63), due to a difference of 0·2 ng/dL between treatment groups (p=0·027). However, oestradiol levels remained well within the normal range for men (0·8–3·5 ng/dL). As the small percent increase in serum oestradiol observed in the finasteride group was similar to the small percent increase in serum testosterone in these patients, the normal ratio of T to oestradiol was unaltered. The small rise in serum oestradiol levels with finasteride use is not unexpected as finasteride produces a small increase in serum testosterone which is the primary substrate for the production of oestradiol in men.

In a study of prolonged exposure to testosterone for up to 3 years in healthy older men (n=69) with low serum testosterone levels, total oestradiol as well as testosterone was found to be significantly increased in both the testosterone-only and tstosterone+5 mg finasteride groups, compared to placebo and baseline values at both 6 and 36 months (Vaughan *et al*., 2007). Total oestradiol levels in the testosterone+finasteride group had increased from (mean ± standard error) 85 ± 34 pmol/L at baseline to 125 ± 57 pmol/L following 6 months' treatment, to 154 ± 74 pmol/L after 36 months. Total oestradiol levels were also significantly higher at 36 months for the testosterone+finasteride group (154 ± 74 pmol/L) compared to both the testosterone-only (123 ± 62 pmol/L) and placebo (79 ± 36 pmol/L) groups (p<0·05).

A similar effect has also been observed in females. In a study that compared the clinical efficacy and safety of 5 mg/day (n=27) and 2·5 mg/day (n=29) finasteride for the treatment of hirsutism in women, the 5 mg/day dose increased serum oestradiol concentrations from 61·8 ± 35·5 pg/mL to 82·8 ± 39·6 pg/mL (p<0·02) following six months of treatment (Bayram *et al*., 2002). The effect was even greater at 12 months with oestradiol concentrations increasing from 61·8 ± 35·5 pg/mL to 94·0 ± 37·5 pg/mL(p<0·0001).

These data are of particular importance as there is evidence which supports an important role of endogenous oestrogen levels in the development of hormone-dependent breast cancer (Casagrande *et al.*, 1988; Suzuki *et al*., 2008).

3.3.2 Clinical trial data – Proscar (5 mg finasteride)

In total there have been 11 reports of breast cancer among males enrolled in 5 mg finasteride clinical trials. However three of these cases occurred in placebo-treated patients; two enrolled in the PLESS trial (McConnell *et al*., 1998), and one enrolled in the PCPT trial (Thompson *et al.*, 2003). The remaining eight cases were with 5 mg finasteride .

Controlled Clinical Trials

Medical Therapy of Prostatic Symptoms (MTOPS)
In the MTOPS trial, 3047 patients were randomised to a double-blind, multi-centre, placebo-controlled clinical trial for 4–6 years (mean 4·5 years; McConnell *et al*., 2003). The treatments were: placebo; 8 mg doxazosin; 5 mg finasteride; and a combination of 8 mg doxazosin and 5 mg finasteride. Three cases of breast cancer occurred in the finasteride-treated group and one case of breast cancer occurred in the combination group. Two of the finasteride cases and the combination-treated case occurred during the double-blind study with onset times from randomisation of 3·4 years, 1·8 years and 4·8 years respectively. The fourth case was discovered in follow-up, after completion of the study (time from randomisation to onset was 5 years).

The temporal relationship in these cases makes a causal association with finasteride possible. Furthermore, no predisposing factors were identified. The occurrence of four cases of breast cancer in this study involving 3047 patients is high considering the incidence in the general population of one case in 100 000 man-years (Sasco *et al*., 1993). Another publication commenting on this study suggests that the rate of breast cancer with finasteride in this study is nearly 200 times the rate in the general population (Lee & Ellis, 2004).

PROSCAR Long Term Efficacy and Safety Study (PLESS)
In the PLESS study, 3040 men were randomised in approximately equal proportions to receive either 5 mg finasteride or placebo for up to 4 years (McConnell *et al*., 1998). In this study, there were no cases of male breast cancer reported in finasteride-treated subjects, and two cases reported in placebo-treated subjects (as mentioned at the beginning of this section).

Prostate Cancer Prevention Trial (PCPT)
In the PCPT study, 18 882 men aged 55 years or older with a normal digital rectal examination and a prostate-specific antigen (PSA) level of 3 ng/mL or lower were randomised to treatment with 5 mg/day finasteride (n=9423) or placebo (n=9459) for 7 years (Thompson *et al.*, 2003). Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4 ng/mL or if a digital rectal examination was abnormal. The primary endpoint was the prevalence of prostate cancer during the 7 years of the study. One case of breast cancer was reported as an adverse experience in each treatment group during the study. The temporal relationship of 7 years makes a causal association in the finasteride case possible. However, a similar time to onset of 6 years was observed in the placebo case. In this very large long-term study, an increased incidence of breast cancer in the finasteride group compared to placebo was not observed.

Other placebo-controlled clinical trials of one year or greater in duration

No incident cases of breast cancer were observed in either Proscar or placebo groups during controlled periods of 1-year- or 2-year placebo-controlled trials.

Uncontrolled open-label extensions
There were two cases of male breast cancer in patients who received finasteride in uncontrolled open-label extension periods of the phase III trials. There were no reports of preceding gynaecomastia in either case. These additional cases with exposure periods of 19 months and 63 months, respectively, suggest that a causal association of finasteride with breast cancer cannot be excluded.

Short-term placebo-controlled studies
Although a number of shorter-term (less than 1 year), placebo-controlled clinical trials with finasteride were conducted, these were not included in the analyses because they were considered less relevant for breast cancer ascertainment due to their short duration. There were no reports of breast cancer in any of these studies with the exception of one patient with recurrent breast cancer (data not published).

For finasteride-exposed patients the total number of patient years of exposure (PYR) from 0–5+ years was 89495.8, and the rate of breast cancer was 7·82 per 100 000 PYR (95% CI 3·73, 16·41). For finasteride-unexposed patients the total number of PYR from 0–5+ years was 78099·0, with a breast cancer rate of 3·84 per 100 000 PYR (1·24, 11·91; p=0·328).

3.3.3. Clinical Trial Data – Propecia (1 mg finasteride)

No cases of breast cancer were reported in men treated with finasteride (primarily 1 mg) for male-pattern baldness in controlled clinical trials up to 5 years in duration, as well as open-extension studies up to 6 years in duration, involving over 4000 men. The majority of studies were conducted in a younger age group than the Proscar studies.

For a similar number of breast cancer cases to be observed with the 1 mg dose as with the 5 mg dose the exposure period would need to be greater for the lower dose. Additionally, the background incidence of male breast cancer is rarer in younger age groups making it less likely to be detected in a sample size of 4000 men.

3.4 Prescription event monitoring (PEM) study

A Prescription Event Monitoring (PEM) study was conducted by the UK Drug Safety Research Unit (DSRU) on 5 mg finasteride (Wilton *et al*., 1996). This non-interventional observational cohort study, conducted prior to the licensing of 1 mg finasteride (Propecia), contained data from 14 772 patients who were issued prescriptions for finasteride by their GP between October 1992–February 1994. GPs logged all events recorded in the patients' notes during the specified period into a simple questionnaire known as a 'Green Form', which was sent to them by DSRU. A 63% response rate was received from the 25 562 forms sent. The observation period between issuing the prescription and sending a Green Form was approximately 1 year in duration.

Of the patients, all but five were male (two were female and the gender was unknown for three patients), and the average age was (mean [standard deviation]) 69 (9·2) years. The indication for use in 83% of the cases was prostatism and related conditions, and was unspecified in 15%, although one female was treated with finasteride for hirsutism.

During this period 95 events with finasteride use were reported as ADRs in 75 patients. The most frequent ADR reported was impotence, with impotence or ejaculatory failure occurring in 2.1% of the cohort. Gynaecomastia and related conditions occurred in 0·4% of the cohort; 17 patients experienced other unspecified breast disorders and mastalgia occurred in four patients.

A total of 33 events concerning malignancies were reported in patients, of these, two were reported as breast carcinoma. For one of the events the time to onset from commencement of finasteride treatment was recorded as 5 months, the other was unknown. Four events of non-malignant breast tumour were also recorded but no further information is known about these cases[a].

The PEM study concludes overall that that finasteride is acceptably safe when used in accordance with the current prescribing information. However, it is not possible from this study to evaluate the cases of breast cancer and their causal relationship with finasteride, as not enough data are available regarding the two events of breast carcinoma and four events of non-malignant breast tumour. Furthermore, the short period of observation limits the possible number of cases which could be identified within this period.

[a] Unpublished data taken from the PEM study report

4. LITERATURE REVIEW

The medical literature from 1992 (first product launch) to 2008 was searched using the search criteria ‘male breast cancer’ and ‘finasteride’ or ‘dutasteride’. In total, five articles and four letters to journal editors were identified and are described below:

- A publication on the MTOPS trial (McConnell *et al*., 2003) described four cases of breast cancer in men on finasteride (reviewed in section 3.3.2). Three letters to the editor referencing these breast cancer reports were written in response to this publication.

Comments: The four cases of breast cancer occurring in the finasteride and the combined finasteride and doxazosin treatment groups of the MTOPS clinical trial are considered to be due to chance by the authors. However, the first letter referencing these describes an additional 13 cases in the US Food and Drug Administration (FDA) database of men developing breast cancer between 1992–2003 while receiving treatment with finasteride for BPH (Wysowski & Farinas, 2004). The median age was 66 years and the time to onset from finasteride use to diagnosis of breast cancer was 21 months. Gynaecomastia was also recorded in four of the cases. Sixteen reports were also received from worldwide sources. Importantly, the authors highlight that there are no breast cancer cases on the FDA database for other drugs used to treat BPH and the number of reports of breast cancer associated with finasteride is disproportionally represented, exceeding the number of reports of breast cancer with any other drug on the database.

In the authors’ response to the first letter (Roehrborn, 2004), data on the number of reports of breast cancer observed in other clinical trials for finasteride were provided, including two cases of breast cancer identified in the placebo group in PLESS study which had approximately the same sample size and study duration as the MTOPS trial. However in the longer (7-year) PCPT trial, one case of breast cancer was diagnosed in both the finasteride and placebo arms of the trials. This study involved more than 18 000 participants and had a much longer follow-up. The authors also suggest that a disproportionately high number of cases may be on the FDA database as more physicians perform breast examinations on men receiving finasteride, because of the increased incidence and known side-effect of gynaecomastia associated with this drug. Roehrborn acknowledges that further investigation is desirable, but notes that other large-scale trials have not found an association between finasteride and male breast cancer.

The third letter is an individual case report of breast cancer by one of the MTOPS study participants and his GP (Lee & Ellis, 2004). This male patient, who was described as previously healthy with no family history of cancer, developed lymph node-positive oestrogen and progesterone receptor-positive breast cancer. The authors consider there to be a causal association and draw attention to the rate of breast cancer in the MTOPS study for finasteride alone and for finasteride and doxazosin combined as being nearly 200 times that of the general population.

- Wallace *et al*. (2001) describe a series of three cases of male breast cancer in patients taking selective serotonin reuptake inhibitors (antidepressants). One of these patients had started finasteride immediately prior before his diagnosis of breast cancer, but finasteride was not thought by the authors to be related to the diagnosis in this patient.

- A review by Ekman, 1998 of the safety of finasteride concluded that there was no association between finasteride and breast cancer and no cases were cited in this article. The article refers to a previously published letter (Green et al, 1996) describing the two cases documented on the FDA database at that time.

In an update and review article on finasteride use from 1992–1995; two cases of male breast cancer are described (Cather *et al*., 1999). One case was diagnosed in a male aged 59 years after 35 days of finasteride treatment, and was thought to be unrelated to drug therapy as typically a longer onset period is needed for the two to be causally related; the other was diagnosed in a 63 year-old male after 21 months of treatment. In a letter to the editor predating this review article, the two cases referenced in the review were described in detail by the authors (Green *et al.*, 1996).

- The literature search showed that dutasteride is used less than finasteride, and fewer cases of breast cancer are reported with its use compared with finasteride, yet a warning that cases of male breast cancer were observed in clinical trials both with dutasteride (2) and placebo (1) has been included in the product information.

5. DISCUSSION

5.1 Data

For the past 10 years the risk of breast cancer with finasteride has been kept under close review by the MHRA. An increase in the number of these ADR case reports prompted a review.

Fifty worldwide male breast cancer cases with 5 mg finasteride (Proscar) and three cases with Propecia (two cases with 1 mg finasteride and one case where the dose of Propecia was unknown) have been reported after licensing to the MAH. Although finasteride is not indicated for use in women, four cases of breast cancer in females have also been reported, one with Proscar and three with Propecia. For cases in which the onset time was specified, 27 of the cases occurred at least 1 year after starting finasteride therapy; four cases occurred within 1–2 years, six cases within 2–3 years, five cases within 3–4 years, three cases within 4–5 years and nine cases occurred after at least 5 years. The time to onset in 14 cases was unknown and nine cases occurred less than 1 year after starting finasteride therapy. The onset times appear to be shorter in the female cases (6 months, 9–10 months, 1 year and one unknown). It could be hypothesised that the difference in endogenous hormone levels between men and women means that a lower dose of finasteride over a shorter period of time in a female may be equivalent to a higher dose over a longer period in a male to produce a similar level of risk, although this is not proven.

A review of the data from UK reported cases of ADRs provides further evidence that finasteride has an effect on the breast which is not related to the underlying conditions BPH or androgenetic alopecia. Levels of reporting are influenced by a variety of factors such as the seriousness of the reaction; whether the reaction is included in the product information; the length of time a drug has been on the market; and promotion or publicity about the medicine or the reaction. Although reporting for individual drugs cannot be directly compared, the data can suggest whether a particular drug appears to have a higher level of reporting than others with similar indications. A comparison of ADRs related to breast cancer occurrence for drugs indicated for BPH demonstrated that 5 mg finasteride was associated with the greatest number of ADRs in each breast cancer-related SOC. While finasteride currently has the second highest usage in the UK for the treatment of BPH, a comparable level of ADR reporting was not observed for any of the other products used for BPH, including tamsulosin which has the highest UK usage. A similar effect was observed when comparing 1 mg finasteride with minoxidil and triamcinolone indicated for alopecia.

In particular the number of cases of gynaecomastia is much greater for finasteride, compared with other treatments. Finasteride is known to cause gynaecomastia and this may be linked to the increased reporting of breast cancer cases (ie, patients who develop gynaecomastia are more likely to have their breasts checked, and therefore the rates of detection of breast cancer in these patients would be higher). However there is currently no strong evidence to suggest that gynaecomastia is a precursor to breast cancer as it occurs in only 9% of breast cancer cases (Fentiman, 1990), but has been reported in up to 50% of men in the general population (Scheike & Visfeldt, 1973).

From the clinical trial data, four cases of breast cancer (three cases with finasteride and one case with finasteride plus doxazosin) were identified in the placebo-controlled MTOPS trial (McConnell *et al*., 2003). The four cases in this study of 3047 patients is

higher than expected as the incidence in the general population is one breast cancer case in 100 000 man-years (Sasco *et al.*, 1993).

In the PLESS study involving 3040 men there were two cases of breast cancer reported in placebo-treated subjects but none in finasteride-treated subjects over a 4-year period (McConnell *et al*., 1998). One of these cases involved a placebo-treated patient with a history of basal cell carcinoma. There was no difference in breast cancer rates reported in the PCPT study involving 18 882 men over a period of 7 years; one case was reported in the finasteride group and a second case in the placebo group, with onset times of 7 and 6 years, respectively (Thompson *et al.*, 2003).

When the incidence rates of breast cancer in clinical trials of greater than 1 year in duration were compared in finasteride-exposed (n=7) and unexposed patients (n=3), the overall incidence rates were 7·82 per 100 000 patient-years of exposure (PYR) (95% CI: 3·73, 16·41) and 3·84 per 100 000 PYR (1·24, 11·91) respectively (p=0·328) (section 3.4.2). For 1 mg finasteride, no cases of breast cancer were observed in over 4000 men, in controlled clinical trials up to 5 years in duration, and open-extension studies up to 6 years in duration. For a similar effect on breast cancer rates to be observed with the 1 mg dose as for the 5 mg dose, it is expected that the exposure period and onset times would need to be greater.

Two cases of breast carcinoma (onset times 5 months and unknown, respectively), and four cases of non-malignant breast tumour were identified in the UK PEM Study which collated data from 14 772 patients up to 1 year after finasteride prescriptions were issued (Wilton *et al*., 1996; section 3·4). The short observation period limits the number of cases which could be identified in this study; however the study highlights the significant underreporting of ADRs to the MHRA.

5.2 Potential biological mechanism of breast cancer development with finasteride use

The main risk factors for the development of male breast cancer include age, family history of breast cancer, inherited gene mutations, Klinefelter's syndrome, radiation exposure, alcohol, chronic liver conditions such as cirrhosis, liver disease leading to hyperoestrogenism, oestrogen treatment, obesity, conditions affecting the testicles (undescended testes, congenital inguinal hernia, orchiectomy, orchitis, testicular injury) and certain occupations such as working in hot environments or exposure to gasoline fumes[a]. Other risk factors include benign breast conditions such as nipple discharge, breast cysts and breast trauma, and Jewish ancestry (Giordano *et al*., 2002). Breast cancer has not been reported in men with genetic deficiency of type II 5α-reductase, suggesting a lack of association between long-term suppression of DHT via the type II 5α-reductase enzyme and the development of breast cancer in men. In addition, men with this genetic deficiency also do not experience male pattern hair loss (Zhu *et al*., 1998). Many of the risk factors for breast cancer in men involve abnormalities in oestrogen and androgen balance, which indicates that male breast cancer may be hormonally driven.

Oestrogens in men are derived from conversion of testosterone to oestradiol and androstenedione to oestrone in adipose tissue. A publication (Thomas *et al.*,1992) hypothesises that the risk of breast cancer is a function of the number of susceptible cells. Breast cells normally grow and divide in response to hormones such as oestrogen.

[a] http://www.cancerhelp.org.uk/type/breast-cancer/about/types/breast-cancer-in-men (Accessed 17/11/09)

Normally men have a very low risk of breast cancer as they have little breast epithelium compared to women; however men with increased oestrogen or reduced androgen levels are at greater risk of breast cancer than other men, and such hormonal changes would be expected to enhance growth of the mammary epithelium. Some clinical investigations have observed higher urinary oestrogen excretion and serum oestradiol levels in men with breast cancer compared to those without breast cancer (reviewed by Thomas *et al*., 1992). The important role of oestrogen in the development of hormone-dependent breast cancer is further supported by the use of oestrogen-deprivation therapies as effective treatments (Suzuki *et al*., 2008). Reduction of oestradiol-binding to the oestrogen receptor is accomplished either by using the antioestrogen tamoxifen or using anastrozole (an aromatase antagonist) which reduces the amount of oestradiol present in the breast cancer cells.

Numerous studies in cultured cells and animals with oestradiol and its metabolites provide support for the hypothesis that oxidative metabolites of oestrogen have genotoxic, mutagenic, transforming and carcinogenic potential and therefore could initiate or cause cancer in humans (reviewed by Yager & Davidson, 2006). A publication in the literature (Friedman 2007) suggests a model in which a sufficiently high local level of oestradiol results in telomerase activity. The telomerase activity allows cell division and may, together with other factors, lead to breast cancer which will proliferate if the rate of cell division is greater than the rate of cell death. In support of this mechanism, telomerase activity has been found in 88% of ductal and lobular breast carcinomas (Shay & Bacchetti, 1997).

In relation to finasteride, the most plausible mechanism for an increased risk of breast cancer with its use is related to its ability to increase endogenous testosterone and thus oestradiol levels. Finasteride is known to inhibit type II 5α-reductase which metabolises testosterone into dihydrotestosterone. As oestrogens in men are derived from conversion of testosterone to oestradiol and androstenedione to oestrone, an increase in testosterone with finasteride use leads to a rise in oestradiol levels due to decreased testosterone metabolism. This was evident in clinical trials with an observed increase in serum testosterone levels of 10–20% with 5 mg finasteride, and similarly an increase in serum testosterone of 13% observed with 1 mg finasteride, although both levels remained within the normal range (section 3.4.1). No significant change in serum oestradiol was found in initial studies with 5 mg finasteride, but this was most likely due to not using a sensitive assay. In contrast, a Propecia study (which used a more sensitive assay than the original 5 mg finasteride studies) demonstrated a significant increase in serum oestradiol levels from baseline in the finasteride group when compared to placebo (p=0·027). Importantly, recent studies have shown that 5 mg finasteride increases oestradiol levels both in males (Vaughan *et al*., 2007) and females (Bayram *et al*., 2002) and that this effect is cumulative with time (section 3.4.1). Although there is no observed change in the testosterone:oestradiol ratio, the changes in hormone levels could have implications for potentially increasing the risk of breast cancer.

5.3 Conclusions

On the basis of the review, the Commission on Human Medicines[a] and their expert advisory group (the Pharmacovigilance Expert Advisory Group[b] advised that an

[a] An independent body which gives advice to UK government Ministers on the safety, quality and efficacy of medicines

[b] A group of medical and scientific experts on pharmacovigilance who advise on, and support, the work of the Commission on Human Medicines

increased risk of male breast cancer with finasteride use cannot be excluded. This advice was endorsed by the Pharmacovigilance Working Party[a]. Patients should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain or nipple discharge because these may be signs of a serious condition, such as breast cancer. In addition, the following wording on the risk of breast cancer with finasteride use will be added to the Summary of Product Characteristics and Patient Information Leaflets for Proscar and Propecia:

Proscar SPC wording:

Section 4.4 Special warnings and precautions for use
Breast cancer in men
Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and in the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Section 4.8 Undesirable Effects
In addition, the following has been reported in clinical trials and post-marketing use; male breast cancer (see 4.4 Special warnings and precautions for use).

Propecia SPC wording:

Section 4.4 Special warnings and precautions for use
Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period.
Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Section 4.8 Undesirable Effects
In addition, the following have been reported in postmarketing use: persistence of erectile dysfunction after discontinuation of treatment with PROPECIA; male breast cancer (see 4.4 Special warnings and precautions for use).

Proscar and Propecia PIL wording:

Possible side effects
You should promptly report to your doctor any changes in your breast tissue such as lumps, pain or nipple discharge as these may be signs of a serious condition, such as breast cancer.

[a] A group who provide recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

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7. GLOSSARY

5α-reductase
An **enzyme** that converts **testosterone** into the more potent **hormone dihydrotestosterone**

Active treatment
The drug that is being evaluated in a study

Adenocarcinoma
A **malignant** tumour that originates in structures in the body called glands

Adipose
Tissue in the body that is made of fat cells

Adjuvant
A substance that is given in addition to a medicine or a vaccine, to enhance their activity. The substance has no direct effect by itself.

Alpha adrenoceptor (blocker)
A protein on a cell or nerve, to which chemicals in the body called catecholamines bind. The blocker also binds to this protein and produces effects such as contraction of blood vessels and an increase in blood pressure

Anastrozole
An **aromatase inhibitor** given to treat breast cancer

Antagonist
A substance that blocks the action of another in the body

Androgen
A group of hormones that stimulate the development of male sex organs

Androstenedione
An **androgen** produced by a structure in the body called the adrenal gland

Aromatase
An **enzyme** that converts **testosterone** to **oestrogen**

Aromatase inhibitor
Drugs that inhibit the action of **aromatase**, and are used to treat advanced **oestrogen**-dependent breast cancer in women who have gone through the menopause

Benign
A tumour that is non-**malignant** or non-**cancerous**

Bimodal
A distribution of events where two values peak and are more frequent than others

BRCA1/2 gene
A **gene** that increases the risk of women getting breast and ovarian cancer, and men getting breast and prostate cancer.

Carcinoma

Cancer originating in the **epithelium**

Chemotherapy
The prevention or treatment of diseases such as cancer, using chemical substances

Chromosome
A piece of DNA found in cells that contains many **genes**

Clinical study
A research study that tests medicines in humans

Congenital inguinal hernia
A condition present at birth, where fat or part of the lower digestive tract protrudes from its normal position through a weak part of the stomach wall

Dihydrotestosterone
A product formed from the action of **5α-reductase** on **testosterone**

Doxazosin
An **alpha-adrenoceptor antagonist**, used to treat high blood pressure and relieve urinary retention due to BPH

Dutasteride
A drug used to treat BPH

Endogenous
Arising within, or derived from, the body

Engorgement
Where a structure in the body is filled with fluid, eg blood

Enzyme
A protein in the body that speeds up biological reactions

Epidemiology
The study of the occurrence, distribution and control of a medical condition or disease in a population

Epithelium
Tissue that lines the skin and internal organs of the body

Follicle-stimulating hormone
A **hormone** that stimulates egg development in women and sperm production in men

Genes
A unit of a **chromosome** made of material called DNA. Genes are found in every cell in the body, and determines the proteins that the cell should produce and an individual's unique traits

Gland
One of several organs or groups of cells in the body that produce certain substances, which are either used by the body or are excreted. A type of gland called an endocrine gland produces **hormones**

Gynaecomastia

Enlargement of breasts in men, either due to a hormone imbalance or to certain drug treatments

Hirsutism
Abnormal hairiness

Hormone
A substance produced by one part of the body that travels to another part of the body and causes a **physiological** effect

Hyperplasia
An increased production and growth of normal cells in body tissue or organs seen in conditions such as BPH

Impotence
Inability of a man to achieve an erection

Incidence
The number of new episodes of an illness or medical condition that occurs in a specific population over a specific period

Indication
Any of the conditions for which a particular medicine may be prescribed, as defined by its licence

Klinefelter's syndrome
A genetic disorder in men, characterised by sexual abnormalities such as small testicles, gynaecomastia and reduced fertility

Luteinising hormone
A **hormone** that stimulates egg release from the ovaries in women

Malignant
Describes a tumour or cancer that invades, spreads and destroys tissue in the body

Mammary
Related to the breast

Mastalgia
Pain in the breast

Mastectomy
Surgical removal of a breast

Median
An average: the middle value in a range of values in a sample

Metabolism
The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

Minoxidil
A drug used to treat several conditions, including hair loss

Neoplasms

A **benign** or **malignant tumour**

Oestradiol
A type of **oestrogen hormone** that is produced by the ovary

Oestrogen
A **hormone** that controls female sexual development

Oestrone
A female sex **hormone**

Off-label
Prescribing a drug for a condition or disease that is not listed in the product's information leaflet, based on a health professional's judgement.

Orchiectomy
(Also spelt 'orchidectomy') Surgical removal of a testicle

Orchitis
Inflammation of the testicle

Paget's disease (of the breast)
A **malignant** condition of the nipple, associated with underlying breast **cancer**

Pathology
The study of disease

Patient-years
The total number of years that a patient in a study has been under observation, eg, the number of years that a patient is treated with a certain drug

Pharmacovigilance
Identifying, assessing and responding to safety issues that emerge for medicines used in clinical practice

Physiological
Normal body function (not related to disease)

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Progestational
Referring to the time after egg release in a woman, when the body produces **progesterone** and is ready for pregnancy

Progesterone
A **hormone** that prepares the body for pregnancy

Prostate
A male sex **gland**

Prostatectomy
Surgical removal of the **prostate gland**

Prostate-specific antigen
A protein produced by the **prostate**. Levels of this protein are increased when the prostate is enlarged or inflamed, and are significantly higher than normal in prostate cancer

Radiotherapy
Treatment of disease with a machine that produces radiation, such as an X-ray machine

Randomised controlled trials
A **clinical trial** in which the study participants are randomly assigned to receive either the test medicine or either a **placebo** or comparator medicine

Serum
The clear component of blood

Substrate
The substance that an **enzyme** acts upon

Tamoxifen
A drug used to treat breast **cancer**

Tamsulosin
An **alpha adrenoceptor antagonist** used to treat symptoms of BPH

Telomerase
An **enzyme** that controls the replication of telomeres, which are the end parts of **chromosomes**

Temporal
Related to time

Testosterone
The main male sex **hormone**, which is part of the **androgen hormone** group

Transurethral
Passing through, or performed via, the tube that transports urine from the bladder to outside the body

Tumour
An abnormal swelling in the body

Ulceration
Production of an ulcer: a break in the epithelium or the membrane lining the digestive tract

Urinary flow rates
Measure of the quantity of urine produced in a specific period

Urinary retention
Inability to pass urine from the bladder, usually due to an obstruction