Benign prostatic hyperplasia (BPH) is a term that describes a prostate which is measurably larger than normal. The condition affects around 50% of men over the age of 60 years. For around 25% of these men lower urinary tract symptoms (LUTS) will accompany BPH. LUTS are partially attributable to an enlarged prostate, as well as to other comorbidities (such as cardiac disease, renal disease and neuromuscular changes within the bladder).

Function of the prostate

The normal prostate gland is around 4cm in diameter and has an average weight of 20g. It is a doughnut-shaped organ that is located inferior to the urinary bladder and encircles the prostatic urethra. The development of LUTS is directly related to the location and orientation of the prostate — prostatic enlargement contributes to alteration in urinary flow rates and, for some patients, acute urinary retention.

The prostate produces mildly acidic secretions that make up around 25% of the seminal volume. These secretions improve the chances of sperm reaching and fertilising an egg by providing the following:

- Citric acid — used in oxidative metabolism, which provides sperm with energy
- Proteolytic enzymes — such as prostate specific antigen (PSA), pepsinogen and hyaluronidase, which help facilitate sperm motility via liquefaction of seminal fluid
- Seminal plasmin — contributes to sperm motility and also has potent antimicrobial activity, thereby reducing the number of naturally occurring bacteria in the ejaculate and the lower section of the female reproductive tract

PSA Serum PSA is used as a marker for both benign and malignant prostatic hyperplasia. It is used in the diagnosis and monitoring of prostate cancer but is insufficiently reliable as a marker to make widespread screening useful. For example, some men with BPH have a high PSA and some men with early malignant disease will have a low PSA. Ultimately, a low PSA does not rule out malignant disease. Due to this lack of specificity, it is difficult for practitioners and men to make informed decisions based upon a PSA result alone. In addition, the investigations that are undertaken after discovering that a man has an
Pathophysiology

The cause and pathophysiology of BPH are still largely unclear. Although there is no doubt that ageing plays a considerable role, a number of other factors appear to be associated with the development of BPH. BPH is likely to be caused by the interplay of the factors discussed below.

Age

There is overwhelming evidence to suggest that as men age there is an increase in the size of the prostate and the incidence of lower urinary tract symptoms. Some studies investigating men without prostate cancer have shown an increase in prostatic volume of 2.5% per year. However, there is not a direct relationship between the size of the prostate and the severity of LUTS. BPH is not the only factor contributing to the development of LUTS; rather it is part of a set of issues — some of which are age related — that affect the ability to store and void urine. The rate of urinary flow declines with increasing age, with men over the age of 70 years experiencing a more rapid decline.

Age is associated with the development of BPH, irrespective of whether or not men exhibit symptoms; more than 90% of all men will eventually develop histopathological changes consistent with BPH.

Tissue remodelling

There is evidence that a tissue-remodelling process causes basal cells in the prostate to become hypertrophic. These changes occur as a result of alterations in cell signalling between stromal and epithelial cells. In addition, in BPH the balance of cell proliferation and apoptosis shifts in favour of proliferation. Increased expression of transforming growth factors β1 and Bcl-2 may explain this shift; both are involved in the normal apoptotic control mechanisms within the prostate.

Research on BPH tissue has demonstrated that BPH cells become hypertrophic and survive longer than those in a healthy prostate.

Hormonal effects

Androgens do not directly cause BPH, but contribute to its development. Men who are castrated before puberty or who have a genetic deficiency in 5α-reductase do not develop BPH. Dihydrotestosterone (DHT) is the metabolite of testosterone and is generated via the action of 5α-reductase, which is secreted from stromal and basal epithelial cells. Some studies have identified increased DHT levels and elevated expression of a number of androgen-dependent genes in BPH tissue compared with normal prostate tissue, although the effect of altered androgen activity is not fully understood.

The effects of oestrogen on the prostate have also been studied, but to a lesser extent than the effects of androgens. As men age their levels of circulating oestrogen remain constant, however, factors such as age-related declining levels of testosterone and excess body fat can alter the ratio of testosterone to oestrogen (in favour of oestrogen). It has been observed that BPH tissue has relative up-regulation of oestrogen receptor alpha and, therefore, the altered ratio of androgen to oestrogen stimulates growth.

Metabolic effects

There is a link between the metabolic syndrome and BPH. Men with the metabolic syndrome have been shown to have faster growing BPH than men with BPH who do not have the condition. The same is true for men with elevated blood pressure, insulin...
resistance, obesity or low levels of high-density lipoprotein cholesterol compared with those who do not have these comorbidities. 

**Inflammation** The role of inflammation in promoting growth within the prostate has been investigated in several studies. Chronic inflammation of prostate tissue has been identified in BPH, and higher levels of inflammation were associated with larger prostates and higher PSA levels.

It is suggested that constant inflammatory activity and subsequent cytokine release leads to cell destruction and the subsequent triggering of a healing response. This healing response is closely related to the hyperproliferative effects seen within enlarged prostate glands. This proliferative environment has also been shown to give rise to hypoxia based upon local demands for oxygen by growing cells. This directly promotes angiogenesis and growth in response to a number of growth factors, including vascular endothelial growth factor.

**Symptoms**

Patients with BPH are not always symptomatic. Indeed, with the current public health focus on prostate cancer, many men will be diagnosed after routine prostate screening by their GP or as part of “well man” clinics. Some men prefer not to seek medical advice and others will accept symptoms as an unavoidable part of ageing. Pharmacist can help to raise awareness of the symptoms of BPH and prostate cancer.

Most patients present with LUTS, although there is a lack of convincing evidence to relate prostate size to severity of LUTS. As stated previously, there are other factors that contribute to the development of these symptoms — the best evidence for this is the fact that women also experience LUTS and, for both men and women, there are age-related changes in smooth muscle that affect the function of the bladder and associated structures.

Typically, patients with BPH present with symptoms associated with difficulties voiding the bladder and storing urine (see Box 1). Symptoms associated with voiding or a resistance to urinary flow can be caused by an enlarged prostate or by a weak detrusor muscle. Conversely, storage symptoms can be the result of BPH or overactivity of the detrusor muscle.

Some men will develop urinary retention associated with BPH, which can be acute and is usually very painful. Patients can also present with chronic retention, in which case a painless but palpable bladder develops over an extended period giving rise to the potential for renal failure, hypertension and chronic infection.

**Box 1: Symptoms of BPH**

Although patients with benign prostatic hyperplasia can be asymptomatic, clinical features can include:

** Voiding symptoms**
- Hesitancy, associated with resistance to urinary flow and possibly weak muscle contractions
- Poor urinary flow and associated increase in the time taken to urinate
- Incomplete bladder emptying and the need to visit the toilet on multiple occasions because of this feeling
- Terminal dribbling

**Storage symptoms**
- Urgency, the need to void without the ability to control, may be associated with urge incontinence where urine is involuntarily leaked
- Polyuria during the day and at night
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Zoladex is the only LHRHa to show survival benefits in all 3 stages of prostate cancer (localised, locally advanced, metastatic).1,2

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DOSAGE AND ADMINISTRATION
One depot every 28 days injected subcutaneously into anterior abdominal wall (see bmpC for important additional details). Endometriosis: Treatment for 6 months only. Endometrial thinning: 4 or 8 week’s treatment. Uterine fibroids: Treatment with supplementary ION administration for up to 3 months before surgery. Assisted reproduction: Administered to downregulate the pituitary gland. This will usually take between 7 and 21 days. 3.4mg and 19.6mg Use Adult males (including the elderly). Treatment of metastatic prostate cancer and locally advanced prostate cancer, as an alternative to surgical castration. Adjunct to radiotherapy or neo-adjuvant prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer. Adjunct to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression. Dosage and administration: One 3.6mg depot every 28 days, or one 10.8mg depot every 12 weeks. Injected subcutaneously into anterior abdominal wall. Contraindications (known severe hypersensitivity to active substance or any excipients of this product). Pregnancy and lactation. Precautions and

Warnings: Monitor carefully, patients with known depression or hypersensitivity. Treatment with Zoladex may lead to positive reactions in anti-doping tests. Interactions: Not known. Pregnancy: Do not use. Lactation: Not recommended. Children: Not indicated. Males: Caution in patients at risk of developing urethral, obstruction or spinal cord compression. May cause reduction in bone mineral density; particular caution in patients with additional risk factors for osteoporosis. Preliminary data suggest use in combination with a bisphosphonate may reduce bone mineral loss. Mood changes, including depression reported. May cause reduction in glucose tolerance in patients with pre-existing diabetes mellitus. Consider monitoring blood glucose levels. No data on removal or discontinuation of the implant (10.8mg): Females: 10.8mg not indicated for use. Take care when drafting consent as denial of consent may be increased. Loss of bone mineral density: current data suggest that recovery of bone loss occurs after cessation of therapy. For breast cancer, preliminary data suggest use in combination with tamoxifen may reduce bone mineral loss. When used for endometriosis, addition of HRT shown to reduce bone mineral density loss and vasomotor symptoms. Withdrawal bleeding: Vaginal bleeding during early treatment (< 1 month). If bleeding continues, investigate cause. Assisted Reproduction: For experienced, specialist use only. Use with caution in patients with polycystic ovary syndrome. Ovarian hyperstimulation syndrome (OHSS), associated with use in combination with gonadotrophin reported. Fertile women who use non-hormonal contraceptive methods during treatment, and until 3 weeks after menopause following discontinuation of treatment. Common and Serious Undesirable Effects: *Refer to SPC in relation to other side-effects. Serious: Myllywiky/musculoskeletal, anaphylactic reactions, pulmonary oedema, urticaria, obstruction (malign). Common: Males: Glucose tolerance impaired. Risks decreased, paraesthesia, spinal cord compression, cardiac failure, myocardial infarction, hot flush, blood pressure abnormal, hyperhidrosis, rash, bone pain, erecility dysfunction, gynaecomastia, injection site reaction, bone density decreased. Females: Urinary decreased, mood altered, depression, paraesthesia, headache, hot flush, blood pressure abnormal, hyperhidrosis, rash, arthritis, vulvovaginal dryness, breast enlargement, injection site reaction, tumour flare, tumour pain (on initiation of treatment), bone density decreased. Post-Marketing Experience: Hepatic dysfunction, pulmonary embolism, arterial pneumonia. Legal, Category: POM Basic, RFS, Cost/depot 6.65. (3.6mg) | 12.35 (19.6mg). Further information AstraZeneca UK Limited, 600 Capability Green, Litho, LUL 3LU, UK. Marketing Authorisation Number(s): PL 1790100064 (3.6mg) and PL 1790100065 (19.6mg).

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to AstraZeneca on 0800 783 0033.

References:
2. Zoladex 3.6 mg SPC; September 2010.

Date of preparation: December 2011 1871600.
Diagnosis

The severity of LUTS in men can be quantified using the “International prostate symptom score”. This is an eight-question tool created in 1992 by the American Urological Association. It asks patients to rate their urinary symptoms on a scale of 1–5, and to rate the effect of the symptoms on their quality of life on a scale of 1–6. The scores are then quantified as follows:
- 0–7: mild LUTS
- 8–19: moderate LUTS
- 20–35: severe LUTS

Guidance published by the National Institute for Health and Clinical Excellence makes specific recommendations around how patients with LUTS should be managed when they present initially, which include:17

- Assessment of medical and drug history
- Physical examination, including assessment of the bladder and a digital rectal examination (DRE)
- Urine dipstick test to detect blood, glucose, protein, leucocytes and nitrates (with the aim of identifying infection or haematuria)
- Completion of a urine frequency chart
- Assessment of serum creatinine if renal impairment is suspected (typically for patients with a palpable bladder or who have had recurrent urinary tract infections, which is indicative of chronic urinary retention)
- Assessment of fluid input and output
- Simple observations of how fluid intake affects symptoms (eg, overactive detrusor muscle.

Following an initial assessment, patients can be offered lifestyle advice and this may be the only intervention required for patients whose LUTS are not overly troublesome. In many cases, assessment of fluid input and output can help to identify changes in lifestyle that might improve symptoms.

Simple observations of how fluid intake affects symptoms may be particularly useful; this could relate to both timing and volume of intake. Additionally, identification of medicines that can exacerbate the condition, including any over-the-counter or herbal medicines, can help to address symptoms (eg, sympathomimetic drugs can worsen urinary retention).

Patients whose DRE indicates prostatic enlargement may wish to have their PSA tested. Although a low result cannot definitively rule out prostate cancer, NICE recommends that men be given the choice. In such cases, patients should be counselled with regard to the specificity of PSA testing.

Other features such as feel of the prostate on DRE may help guide a decision with regard to PSA testing — a smooth, evenly enlarged prostate is less likely to be cancerous than a prostate that is irregular in shape and has hard nodules. A patient whose prostate is deemed abnormal on DRE, or whose PSA is elevated, may be referred for specialist assessment. Assessment may include a transrectal ultrasound with or without biopsy of the prostate.

It is recommended that patients with LUTS who require specialist referral undergo urinary flow studies and urodynamic studies. Primarily these investigations are used to help identify which patients will respond best to surgical intervention. Patients with predominantly voiding symptoms (eg, outflow obstruction and low flow rates) respond well to surgical intervention; those with storage symptoms, where there is a higher urinary flow rate, do not.19 Patients with low flow rates of <10ml/s can be reliably diagnosed as having an obstruction to bladder outflow whereas those with flow rates of >15ml/s are more likely to have storage symptoms associated with an overactive detrusor muscle.

Some patients who exhibit haematuria and symptoms of chronic infection of the upper urinary tract (eg, considerable pain) may be referred for cystoscopy to rule out abnormalities beyond BPH.

References