Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Duagen 0.5 mg soft capsules**.**

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg dutasteride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

The capsules are opaque, yellow, oblong soft gelatin capsules imprinted with GX CE2 on one side in red ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

For information on effects of treatment and patient populations studied in clinical trials please see section 5.1**.**

4.2 Posology and method of administration

Adults (including elderly):
The recommended dose of Duagen is one capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole and may be taken with or without food. Although an improvement may be observed at an early stage, it can take up to 6 months before a response to the treatment can be achieved. No dose adjustment is necessary in the elderly.

Renal impairment
The effect of renal impairment on dutasteride pharmacokinetics has not been studied**.** No adjustment in dosage is anticipated for patients with renal impairment *(see section 5.2).*

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment *(see section 4.4 and section 5.2).* In patients with severe hepatic impairment, the use of dutasteride is contraindicated *(See section 4.3 Contraindications).*

4.3 Contraindications

Duagen is contraindicated in:
- women and children and adolescents *(see section 4.6).*
- patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, or any of the excipients.
- patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events and after consideration of alternative treatment options including monotherapies *(see section 4.2).*

Digital rectal examination, as well as other evaluations for prostate cancer, must be performed on patients with BPH prior to initiating therapy with Duagen and periodically thereafter.

Dutasteride is absorbed through the skin, therefore, women**,** children and adolescents must avoid contact with leaking capsules *(see section 4.6).* If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

Dutasteride was not studied in patients with liver disease. Caution should be used in the administration of dutasteride to patients with mild to moderate hepatic impairment *(see section 4.2, section 4.3 and section 5.2).*

Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Generally, a total serum PSA concentration greater than
4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking Duagen does not exclude a diagnosis of prostate cancer. Duagen causes a decrease in serum PSA levels by approximately 50%, after 6 months, in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL). Therefore to interpret an isolated PSA value in a man treated with Duagen for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. Any sustained increases in PSA levels while on Duagen should be carefully evaluated, including consideration of noncompliance to therapy with Duagen.

Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of Duagen. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Duagen therapy, no adjustment to its value appears necessary.

4.5 Interaction with other medicinal products and other forms of interaction

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection, please *see section 4.4.*

Effects of other drugs on the pharmacokinetics of dutasteride

Use together with CYP3A4 and/or P-glycoprotein-inhibitors:

Dutasteride is mainly eliminated via metabolism. *In vitro* studies indicate that this metabolism is catalysed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1.6 to 1.8 times greater, respectively, in a small number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P-glycoprotein) than in other patients.

Long-term combination of dutasteride with drugs that are potent inhibitors of the enzyme CYP3A4 (e.g. ritonavir, indinavir, nefazodon, itraconazole, ketoconazole administered orally) may increase serum concentrations of dutasteride. Further inhibition of 5-alpha reductase at increased dutasteride exposure, is not likely. However, a reduction of the dutasteride dosing frequency can be considered if side effects are noted. It should be noted that in the case of enzyme inhibition, the long half-life may be further prolonged and it can take more than 6 months of concurrent therapy before a new steady state is reached.

Administration of 12g cholestyramine one hour before a 5mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other drugs

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P-glycoprotein. *In vitro* interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

In a small study (N=24) of two weeks duration in healthy men, dutasteride (0.5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamic interaction in this study.

4.6 Pregnancy and lactation

Duagen is contraindicated for use by women.

Fertility

Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men *(see section 5.1).* The possibility of reduced male fertility cannot be excluded.

Pregnancy

As with other 5 alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus *(see section 4.4).*
Small amounts of dutasteride have been recovered from the semen in subjects receiving Duagen 0.5mg/day. Based on studies in animals, it is unlikely that a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with Duagen (the risk of which is greatest during the first 16 weeks of pregnancy).

However, as with all 5 alpha reductase inhibitors, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom.

Lactation

It is not known whether dutasteride is excreted in human milk**.**

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties of dutasteride, treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

4.8 Undesirable effects

Approximately 19% of the 2167 patients who received dutasteride in the 2 year Phase III placebo-controlled trials developed adverse reactions. The majority of events were mild to moderate and occurred in the reproductive system. No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

The following table shows adverse reactions from controlled clinical trials and post-marketing experience. The listed adverse events from clinical trials have been reported with a higher incidence in patients treated with dutasteride compared with placebo during the first year of treatment. Adverse events from post-marketing experience were identified from spontaneous post-marketing reports; therefore the true incidence is unknown:

Organ system	Adverse reaction	Incidence
*Reproductive system and breast disorders	Impotence	6.0%
	Altered (decreased) libido	3.7%
	Ejaculation disorders	1.8%
	Gynecomastia (includes breast enlargement and/or breast tenderness)	1.3%
**Immune system disorders	Allergic reactions including rash, pruritus, urticaria, localised oedema, and angioedema	Unknown

* Incidence from clinical trial data
** Adverse events from post-marketing data

4.9 Overdose

In volunteer studies of Duagen, single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg. There is no specific antidote for Duagen, therefore, in suspected overdosage symptomatic and supportive treatment should be given as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors.
ATC code**:** G04C B02.

Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5α-reductase isoenzymes which are responsible for the conversion of testosterone to 5α-DHT.

DUAGEN AS MONOTHERAPY

Effects on DHT/Testosterone:

Effect of daily doses of Duagen on the reduction on DHT is dose dependant and is observed within 1-2 weeks (85% and 90% reduction, respectively).
In patients with BPH treated with dutasteride 0.5 mg/day, the median decrease in serum DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years.

Effect on Prostate Volume:

Significant reductions in prostate volume have been detected as early as one month after initiation of treatment and reductions continued through Month 24 ($p<0.001$). Duagen led to a mean reduction of total prostate volume of 23.6% (from 54.9ml at baseline to 42.1ml) at Month 12 compared with a mean reduction of 0.5% (from 54.0ml to 53.7ml) in the placebo group. Significant ($p<0.001$) reductions also occurred in prostate transitional zone volume as early as one month continuing through Month 24, with a mean reduction in prostate transitional zone volume of 17.8% (from 26.8ml at baseline to 21.4ml) in the Duagen group compared to a mean increase of 7.9% (from 26.8ml to 27.5ml) in the placebo group at Month 12. The reduction of the prostate volume seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies. Reduction of the size of prostate leads to improvement of symptoms and a decreased risk for AUR and BPH-related surgery.

CLINICAL STUDIES:

Duagen 0.5 mg/day or placebo was evaluated in 4325 male subjects with moderate to severe symptoms of BPH who had prostates ≥30ml and a PSA value within the range 1.5 - 10 ng/mL in three primary efficacy 2-year multicenter, multinational, placebo-controlled, double-blind studies.

The studies then continued with an open-label extension to 4 years with all patients remaining in the study receiving dutasteride at the same 0.5 mg dose. 37% of initially placebo-randomized patients and 40% of dutasteride-randomized patients remained in the study at 4 years. The majority (71%) of the 2,340 subjects in the open-label extensions completed the 2 additional years of open-label treatment.

The most important clinical efficacy parameters were American Urological Association Symptom Index (AUA-SI), maximum urinary flow (Qmax) and the incidence of acute urinary retention and BPH-related surgery.
AUA-SI is a seven-item questionnaire about BPH-related symptoms with a maximum score of 35. At baseline the average score was approx. 17.
After six months, one and two years treatment the placebo group had an average improvement of 2.5, 2.5 and 2.3 points respectively while the Duagen group improved 3.2, 3.8 and 4.5 points respectively. The differences between the groups were statistically significant. The improvement in AUA-SI seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Qmax (maximum urine flow):

Mean baseline Qmax for the studies was approx 10 ml/sec (normal Qmax ≥15 ml/sec). After one and two years treatment the flow in the placebo group had improved by 0.8 and 0.9 ml/sec respectively and 1.7 and 2.0 ml/sec respectively in the Duagen group. The difference between the groups was statistically significant from Month 1 to Month 24. The increase in maximum urine flow rate seen during the first 2 years of double blind treatment was maintained during an additional 2 years of open-label extension studies.

Acute Urinary Retention and Surgical Intervention

After two years of treatment, the incidence of AUR was 4.2% in the placebo group against 1.8% in the Duagen group (57% risk reduction). This difference is statistically significant and means that 42 patients (95% CI 30-73) need to be treated for two years to avoid one case of AUR.

The incidence of BPH-related surgery after two years was 4.1% in the placebo group and 2.2% in the Duagen group (48% risk reduction). This difference is statistically significant and means that 51 patients (95% CI 33-109) need to be treated for two years to avoid one surgical intervention.

Hair distribution

The effect of dutasteride on hair distribution was not formally studied during the phase III programme, however, 5 alpha-reductase inhibitors could reduce hair loss and may induce hair growth in subjects with male pattern hair loss (male androgenetic alopecia).

Thyroid function:

Thyroid function was evaluated in a one year study in healthy men. Free thyroxine levels were stable on dutasteride treatment but TSH levels were mildly increased (by 0.4 MCIU/mL) compared to placebo at the end of one year's treatment.

However, as TSH levels were variable, median TSH ranges (1.4 - 1.9 MCIU/mL) remained within normal limits (0.5 - 5/6 MCIU/mL), free thyroxine levels were stable within the normal range and similar for both placebo and dutasteride treatment, the changes in TSH were not considered clinically significant. In all the clinical studies, there has been no evidence that dutasteride adversely affects thyroid function.

Breast neoplasia:

In the 2 year clinical trials, providing 3374 patient years of exposure to dutasteride, and at the time of registration in the 2 year open label extension, there were 2 cases of breast cancer reported in dutasteride-treated patients and 1 case in a patient who received placebo.
However, the relationship between breast cancer and dutasteride is not clear.

Effects on male fertility

The effects of dutasteride 0.5mg/day on semen characteristics were evaluated in healthy volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all parameters at all time points remained within the normal ranges and did not meet the predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24 week follow-up. The possibility of reduced male fertility cannot be excluded.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%. The bioavailability of dutasteride is not affected by food.

Distribution

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>99.5%).
Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months.
Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Elimination

Dutasteride is extensively metabolized *in vivo*. *In vitro*, dutasteride is metabolized by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite.

Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each). Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine.

The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable.
At low serum concentrations (less than 3 ng/mL), dutasteride is cleared rapidly by both the concentration dependent and concentration independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days.

At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

Elderly

Dutasteride pharmacokinetics were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. No significant influence of age was seen on the exposure of dutasteride but the half-life was shorter in men under 50 years of age. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old.

Renal impairment

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no clinically significant increase of the dutasteride plasma concentrations is anticipated for patients with renal impairment *(see section 4.2).*

Hepatic impairment

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied *(see section 4.3).* Because dutasteride is eliminated mainly through metabolism the plasma levels of dutasteride are expected to be elevated in these patients and the half-life of dutasteride be prolonged *(see section 4.2 and section 4.4).*

5.3 Preclinical safety data

Current studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans.

Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride). The clinical relevance of these findings is unknown.

As with other 5 alpha reductase inhibitors, feminisation of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminisation of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
mono- and diglycerides of caprylic/capric acid
butylhydroxytoluene (E321).

Capsule shell:
gelatin
glycerol
titanium dioxide (E171)
iron oxide yellow (E172)
triglycerides, medium chain
lecithin.

Red printing ink containing iron oxide red (E172) as the colourant, polyvinyl acetate phthalate, propylene glycol and Macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blisters of opaque PVC/PVDC film containing 10 soft gelatin capsules packed into containers of 10, 30, 50, 60 and 90 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Dutasteride is absorbed through the skin, therefore contact with leaking capsules must be avoided. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water *(see section 4.4).*

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
Stonemasons Way
Rathfarnham
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8 MARKETING AUTHORISATION NUMBER

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