

New Zealand Data Sheet

1. PRODUCT NAME

TEROD® 500 micrograms soft gelatin capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 micrograms of dutasteride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TEROD 500 micrograms capsules are light brown, oblong, soft gelatin capsules.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TEROD is indicated for the following:

- treatment of, and to prevent progression of Benign Prostatic Hyperplasia (BPH) by reducing prostate size, alleviating symptoms, improving urinary flow and reducing the risk of acute urinary retention (AUR) and the need for BPH related surgery.
- use as combination therapy in the management of symptomatic BPH with an alpha blocker which is approved for use in BPH and which has been dose titrated in accordance with the relevant recommendation in the product information for that alpha blocker.

4.2. Dose and method of administration

Dose

Adults

The recommended dose is one capsule (500 micrograms) taken orally once a day.

Although an improvement may be observed at an early stage, treatment for at least 6 months may be necessary in order to assess whether a satisfactory response to the treatment can be achieved.

For treatment of BPH, dutasteride can be administered alone or in combination with an alpha-1 adrenergic blocker. Implementation of the combination therapy of TEROD and an alpha blocker requires consideration of the combined side-effect profiles; *see Section 4.4, 4.8 and 5.1.*

Special populations

Elderly population

No dutasteride dose adjustment based on age is necessary, *see Section 5.2.*

Renal impairment:

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, 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, *see Section 4.4.*

Method of Administration

The capsules should be swallowed whole and not chewed or opened, as contact with the capsules may result in irritation of the oropharyngeal mucosa.

TEROD may be taken with or without food.

4.3. Contraindications

TEROD is contra-indicated in:

- patients with known hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, or to any of the excipients listed in section 6.
- women and children, *see Section 4.6*

4.4. Special warnings and precautions for use

Leaking capsules

Dutasteride is absorbed through the skin; therefore, women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water, *see Section 4.3 and 6.6.*

Combination use with an alpha blocker

Implementation of the combination therapy of TEROD and an alpha blocker requires consideration of the combined side-effect profiles. Cardiovascular function should be stabilised prior to initiating combination therapy or adding an alpha blocker to TEROD monotherapy. When initiating less selective alpha blockers such as doxazosin, terazosin and prazosin, careful and measured titration of the dose is required to minimise the risk of alpha blocker-related adverse events such as postural hypotension, dizziness and syncope. Dose titration is normally not required for the selective alpha blockers such as tamsulosin and alfuzosin. Please see the recommendations in the data sheet of the relevant alpha blocker for full safety information.

Combination Therapy with Tamsulosin and cardiac failure

In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low ($\leq 1\%$) and variable between the studies. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established, see *Section 5.1*.

Hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease, see *Sections 4.2 and 5.2*.

Effects on prostate specific antigen (PSA) and prostate cancer detection

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

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer.

Dutasteride causes a decrease in serum PSA levels by approximately 50 %, after 6 months of treatment.

Patients receiving dutasteride should have a new PSA baseline established after 6 months of treatment with dutasteride. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on dutasteride may signal the presence of prostate cancer (particularly high grade cancer) or non-compliance to therapy with dutasteride and should be carefully evaluated, even if those values are still within the normal range for men

not taking a 5-alpha reductase inhibitor (*see Section 5.1*). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with dutasteride does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established, *see Section 5.1*.

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 TEROD. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary.

Prostate cancer and high grade tumours

In a 4-year study of over 8,000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), 1,517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n=29, 0.9 %) compared to the placebo group (n=19, 0.6 %). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between dutasteride and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing, *see Section 5.1*.

Breast cancer in men

Breast cancer has been reported in men taking dutasteride in clinical trials (*see Section 5.1*) and during the post-marketing period. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. It is not clear if there is a causal relationship between the occurrence of male breast cancer and long-term use of dutasteride.

Blood donation

Men being treated with TEROD should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

4.5. Interaction with other medicines and other forms of interaction

Use together with CYP3A4 inhibitors

In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Phase II data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37 %) and diltiazem (44 %). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride.

A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10 times the recommended dose has been given to patients for up to six months); therefore no dose adjustment is necessary.

Effects of dutasteride on the pharmacokinetics of other drugs

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6, *see Section 5.2*.

Dutasteride neither inhibits human cytochrome P450 drug-metabolizing enzymes *in vitro* nor induces cytochrome P450 isoenzymes CYP1A, CYP2B and CYP3A in rats and dogs *in vivo*.

In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant interactions have been observed.

A drug interaction study with tamsulosin or terazosin administered in combination with dutasteride for two weeks showed no evidence of pharmacokinetic or pharmacodynamic interactions.

Although specific interaction studies were not performed with other compounds, approximately 90 % of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

4.6. Fertility, pregnancy and lactation

Pregnancy

TEROD is contra-indicated for use by women. Dutasteride has not been studied in women because preclinical data suggest that the suppression of circulating levels of dihydrotestosterone

may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride, *see Section 5.3*.

Breast-feeding

It is not known whether dutasteride is excreted in breast milk.

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 clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

4.7. Effects on ability to drive and use machines

Based on the pharmacokinetic and 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

Clinical trial data

Table 1: Adverse events in controlled studies of dutasteride monotherapy for BPH

The following investigator-judged drug-related adverse events (with incidence $\geq 1\%$) have been reported more commonly in the three-phase III placebo-controlled studies on dutasteride treatment compared to placebo.

Organ System	Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
		Placebo (n = 2158)	Dutasteride (n = 2167)	Placebo (n = 1736)	Dutasteride (n = 1744)
Reproductive system and breast disorders	Impotence	3%	6%	1%	2%
	Altered (decreased) libido	2%	4%	<1%	<1%
	Ejaculation disorders	<1%	2%	<1%	<1%
	Breast Disorders ⁺	<1%	1%	<1%	1%

⁺ includes breast tenderness and breast enlargement

No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

Table 2: Adverse events in controlled studies of dutasteride and tamsulosin combination therapy

The following investigator-judged drug-related adverse events (with an incidence of greater than or equal to 1 %) have been reported in the CombAT (Combination of Dutasteride and Tamsulosin) Study, a comparison of dutasteride 500 micrograms and tamsulosin 400 micrograms once daily for four years in combination or as monotherapy.

Organ System	Adverse Reaction	Incidence during treatment period			
		Year 1 (n=1610)	Year 2 (n=1428)	Year 3 (n=1283)	Year 4 (n=1200)
	Combination ^a (n)	(n=1610)	(n=1428)	(n=1283)	(n=1200)
	Dutasteride	(n=1623)	(n=1464)	(n=1325)	(n=1200)
	Tamsulosin	(n=1611)	(n=1468)	(n=1281)	(n=1112)
Nervous system disorders	Dizziness				
	Combination ^a	1%	<1%	<1%	<1%
	Dutasteride	<1%	<1%	<1%	<1%
	Tamsulosin	1%	<1%	<1%	0%
Reproductive system and breast disorders	Impotence				
	Combination ^a	6%	2%	<1%	<1%
	Dutasteride	5%	2%	<1%	<1%
	Tamsulosin	3%	1%	<1%	1%
	Altered (decreased) libido				
	Combination ^a	5%	<1%	<1%	0%
	Dutasteride	4%	1%	<1%	0%
	Tamsulosin	2%	<1%	<1%	<1%
	Ejaculation disorders				
	Combination ^a	9%	1%	<1%	<1%
	Dutasteride	1%	<1%	<1%	<1%
	Tamsulosin	3%	<1%	<1%	<1%
	Breast disorders^b				
Combination ^a	2%	<1%	<1%	<1%	
Dutasteride	2%	1%	<1%	<1%	
Tamsulosin	<1%	<1%	<1%	0%	

a Combination = dutasteride 500 micrograms once daily plus tamsulosin 400 micrograms once daily.

b Includes breast tenderness and breast enlargement.

Post-marketing Experience

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1000$) and very rare ($<1/10,000$) including isolated reports. Frequency categories determined from post-marketing data refer to reporting rate rather than true frequency.

Immune system disorders

Very rare: Allergic reactions, including rash, pruritus, urticaria, localised oedema and angioedema.

Psychiatric disorders

Very rare: Depressed mood.

Skin and subcutaneous disorders

Rare: Alopecia (primarily body hair loss), hypertrichosis.

Reproductive system and breast disorders

Very rare: Testicular pain and testicular swelling.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

In volunteer studies, single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In clinical studies doses of 5 mg daily have been administered to patients for 6 months with no additional adverse effects to those seen at therapeutic doses of 500 micrograms.

There is no specific antidote for dutasteride, therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors, ATC code: G04CB02

Pharmacodynamic effects

Dutasteride is a dual inhibitor of 5-alpha-reductase. It inhibits both type 1 and type 2, 5-alpha-reductase isoenzymes which are responsible for the conversion of testosterone to 5 α -dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

Effects on DHT/Testosterone

The maximum effect of daily doses of dutasteride on the reduction on DHT is dose dependent and is observed within 1-2 weeks. After 1 week and 2 weeks of daily dosing of dutasteride 500 micrograms, median serum DHT concentrations were reduced by 85 % and 90 % respectively.

In BPH patients treated with 500 micrograms of dutasteride daily, the median decrease in 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. This is an expected consequence of 5-alpha-reductase inhibition and did not result in any known adverse events.

Clinical efficacy and safety

Dutasteride monotherapy for BPH

Dutasteride 500 micrograms/day or placebo was evaluated in 4325 male subjects with enlarged prostates (>30cc) in three primary efficacy 2-year multicentre, placebo-controlled, double-blind studies.

In men with BPH, dutasteride treats and prevents disease progression by reducing the risk of both acute urinary retention (AUR) and the need for surgical intervention (SI) and by providing statistically significant improvement of lower urinary tract symptoms (LUTS), maximum urinary flow rate (Q_{max}) and prostate volume relative to placebo. These improvements in LUTS, Q_{max} and prostate volume were seen through to 24 months, and LUTS and Q_{max} continued to improve for a further 2 years in open-label extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open-label extension studies.

Dutasteride and tamsulosin combination therapy for BPH

Dutasteride 500 micrograms/day, tamsulosin 400 micrograms/day or the combination of dutasteride 500 micrograms plus tamsulosin 400 micrograms was evaluated in 4844 male

subjects with enlarged prostates (greater than or equal to 30cc) in a multicentre, double blind, parallel group study over 4 years.

The primary efficacy endpoint at 2 years of treatment was the level of improvement from baseline in the international prostate symptom score (IPSS). After 2 years of treatment, combination therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units. The adjusted mean improvements in symptom scores observed with the individual therapies were -4.9 units for dutasteride and -4.3 units for tamsulosin. The adjusted mean improvement in flow rate from baseline was 2.4 mL/sec for the combination, 1.9 mL/sec for dutasteride and 0.9 mL/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for the combination, -1.7 for dutasteride and -1.5 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for combination therapy compared with tamsulosin monotherapy alone.

The primary efficacy endpoint at 4 years of treatment was time to the first event of AUR or BPH-related surgery. After 4 years of treatment, combination therapy statistically significantly reduced the risk of AUR or BPH-related surgery (65.8 % reduction in risk $p < 0.001$ [95 % CI 54.7% to 74.1 %]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2 % for combination therapy and 11.9 % for tamsulosin ($p < 0.001$). Compared to dutasteride monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6 %; the difference between treatment groups was not significant ($p = 0.18$ [95 % CI -10.9 % to 41.7 %]). The incidence of AUR or BPH-related surgery by Year 4 was 4.2 % for combination therapy and 5.2 % for dutasteride.

Clinical progression was defined as a composite of worsening symptoms, (IPSS), and BPH-related events of AUR, incontinence, UTI, and renal insufficiency. Combination therapy was associated with a statistically significantly lower rate of clinical progression compared with tamsulosin ($p < 0.001$, 44.1 % risk reduction [95 % CI: 33.6 % to 53.0 %]) after 4 years. The rates of clinical progression for combination therapy, tamsulosin, and dutasteride were: 12.6 %, 21.5 %, and 17.8 %, respectively.

The statistically significant adjusted mean improvement in symptom scores (IPSS) from baseline was maintained from year 2 to year 4. At 4 years, the adjusted mean improvements in symptom scores observed were -6.3 units for combination therapy, -5.3 units for dutasteride monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in flow rate (Q_{max}) from baseline was 2.4 mL/sec for combination therapy, 2.0 mL/sec for dutasteride monotherapy and 0.7 mL/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Q_{max} was statistically significantly greater with combination

therapy at each 6-month assessment from Month 6 to Month 48 ($p < 0.001$). Compared with dutasteride, the adjusted mean improvement from baseline in Qmax was not statistically significantly different than with combination therapy ($p = 0.050$ at Month 48).

Combination therapy was significantly superior ($p < 0.001$) to tamsulosin monotherapy and to dutasteride monotherapy for the improvement in health outcome parameters BII and BPH-related Health Status (BHS) at 4 years. The adjusted mean improvement in BII from baseline was -2.2 units for the combination, -1.8 for dutasteride and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for dutasteride and -1.1 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 4 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

Cardiac failure

In a 4-year comparison of dutasteride co-administered with tamsulosin and dutasteride or tamsulosin monotherapy in men with BPH (the CombAT study), the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9 %) was higher than in either monotherapy group: dutasteride, 4/1623 (0.2 %) and tamsulosin, 10/1611, (0.6 %). The relative risk estimate for time to first cardiac failure event was 3.57 [95 % CI 1.17, 10.8] for combination treatment compared to dutasteride monotherapy and 1.36 [95 % CI 0.61, 3.07] compared to tamsulosin monotherapy. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established, *see Section 4.4*.

In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study) there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride (30/4105, 0.7 %) versus placebo (16/4126, 0.4 %) for a relative risk estimate for time to first cardiac failure event of 1.91 [95 % CI 1.04, 3.50]. In a post-hoc analysis of concomitant alpha blocker use, there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0 %), compared to subjects not taking dutasteride and an alpha blocker concomitantly: dutasteride and no alpha blocker (18/2953, 0.6 %), placebo and an alpha blocker (1/1399, <0.1 %), placebo and no alpha blocker (15/2727, 0.6 %). No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established, *see Section 4.4*.

Prostate cancer and high grade tumours

In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), 6,706 subjects had prostate needle biopsy data available for analysis to

determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6). There was no difference in the incidence of Gleason 7-10 cancers ($p=0.81$).

There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group ($n=29$, 0.9 %) compared to the placebo group ($n=19$, 0.6 %) ($p=0.15$). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the dutasteride group ($n=17$, 0.5 %) and the placebo group ($n=18$, 0.5 %). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the dutasteride group ($n=12$, 0.5 %) compared with the placebo group ($n=1$, <0.1 %) ($p=0.0035$). There are no data available on the effect of dutasteride beyond 4 years in men at risk of prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the dutasteride group (0.5 % in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1 % versus 0.5 %, respectively). In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were ($n=8$, 0.5 %) for dutasteride, ($n=11$, 0.7 %) for tamsulosin and ($n=5$, 0.3 %) for combination therapy see *Section 4.4*.

Effects on prostate specific antigen (PSA) and prostate cancer detection

In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), dutasteride treatment caused a decrease in mean serum PSA by approximately 50 % after six months of treatment with a large variability (standard deviation of 30 %) among patients. The PSA suppression observed at six months was similar in men who did or who did not develop biopsy-detectable prostate cancer during the study, see *Section 4.4*.

Incidence of breast cancer

In BPH monotherapy clinical trials, providing 3374 patient years of exposure to dutasteride, there were 2 cases of breast cancer reported in dutasteride-treated patients, one after 10 weeks and one after 11 months of treatment and 1 case in a patient who received placebo. In subsequent clinical trials in BPH and 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL providing 17489 patient years exposure to dutasteride and 5027 patient years exposure to dutasteride and tamsulosin combination there were no additional cases in any of the treatment groups. The relationship between long-term use of dutasteride and male breast cancer is unknown.

Effects on male fertility

The effects of dutasteride 500 micrograms/day on semen characteristics were evaluated in normal 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 semen parameters at all time points remained within the normal ranges and did not meet 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 clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known, *see Section 4.6*.

5.2. Pharmacokinetic properties

Dutasteride pharmacokinetics can be described as first-order absorption process and two parallel elimination pathways, one saturable (concentration dependent) and one non-saturable (concentration independent).

Absorption

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 500 micrograms dose, peak serum concentrations of dutasteride occur within 1-3 hours.

Absolute bioavailability in man is approximately 60 % relative to a 2-hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

Distribution

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride 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 500 micrograms once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5 %.

Biotransformation

In vitro, dutasteride is metabolised by the human cytochrome P450 enzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by the CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride), and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The five human serum metabolites of dutasteride have been detected in rat serum, however, the stereochemistry of the hydroxyl additions at the 6 and 15 positions in human and rat metabolites is not known.

Elimination

Dutasteride is extensively metabolized. Following oral dosing of dutasteride 500 micrograms/day to steady state in humans, 1.0 % to 15.4 % (mean of 5.4 %) of the administered dose is excreted as 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.

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 serum concentrations, greater than 3 ng/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with a terminal half-life of 3 to 5 weeks. At therapeutic concentrations, following repeat dosing of 500 micrograms/day, the slower clearance dominates and the total clearance is linear and concentration independent.

Special populations

Elderly population

Dutasteride pharmacokinetics and pharmacodynamics 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. Exposure of dutasteride, represented by AUC and C_{max} values, was not statistically different when comparing age groups.

Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old group which encompasses the age of most men with BPH.

No differences in drug effect as measured by DHT reductions were observed between age groups.

Renal impairment

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1 % of a steady-state 500 micrograms dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied *see Section 4.4.*

5.3. Preclinical safety data

Animal toxicology and/or pharmacology

At exposures greatly in excess of those at the clinical dose, reversible, non-specific CNS related effects were seen in rats (425-fold) and dogs (315-fold).

Reproductive toxicology

Reproductive toxicity findings were consistent with the pharmacological activity of 5-alpha-reductase inhibition. In male rats and dogs, these included effects on accessory reproductive organs and, in male rats, a reversible decrease in fertility. This is considered to have no clinical relevance, as there was no effect on sperm development, concentration or motility. Feminisation of the external genitalia was noted in male fetuses of female rats and rabbits orally dosed with dutasteride. However, intravenous administration of dutasteride to pregnant Rhesus monkeys during embryo-fetal development at doses of up to 2010 ng/animal/day did not produce adverse maternal or fetal toxicity. This dose represents a multiple of at least 186-fold (ng/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100 % absorption) from a dutasteride-treated man.

Carcinogenesis, mutagenesis

Dutasteride was not genotoxic in a wide range of mutagenicity tests.

In a carcinogenicity study in rats, there was an increase in benign interstitial cell tumours in the testis at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

TEROD soft gelatin capsules contain the following excipients: Butylated hydroxytoluene, gelatin, glycerol, iron oxide red, iron oxide yellow, octanoic/decanoic acid glycerides, and titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months from the date of manufacture.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

Cartons of PVC/PVDC- Aluminium blister strips, containing 30 and 90 capsules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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 medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
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9. DATE OF FIRST APPROVAL

05 June 2014

10. DATE OF REVISION OF THE TEXT

20 October 2017

Summary table of changes

Section Changed	Summary of new information
All	Revised to reflect SPC format