1. TRADE NAME OF THE PHARMACEUTICAL PRODUCT
FINASTERIDE MEVON 5MG TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 film coated tablet contains Finasteride 5mg

3. PHARMACOTECHNICAL FORM
Film coated tablets

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic Indications
It is indicated for the treatment of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate, since it reduces the prostate size, leading to improvement of the urinary flow rate and in BPH's symptoms, it reduces the frequency of acute retention of urine and the need for surgical procedure for prostate transurethral resection and prostatectomy.

4.2 Dosage and mode of administration
The recommended dose is 5mg per day, with or without food.

Dosage in renal insufficiency
No dosage readjustment is required in patients with any degree of renal insufficiency (creatinine clearance as low as 9ml/min), and also no change was presented in the disposition of finasteride from pharmacokinetics studies.

Dosage in elderly patients
No dosage readjustment is required, although studies of pharmacokinetics show that the excretion of finasteride is slightly more reduced in patients aged above 70 years old.

Dosage in liver failure
There are no data for the administration of finasteride in patients with liver failure.

4.3 Contraindications
FINASTERIDE MEVON 5MG TABLET is contraindicated in women or children.
FINASTERIDE MEVON 5MG TABLET is contraindicated in the following cases:
- Hypersensitivity in any component of the drug.
- Pregnancy. Finasteride is contraindicated in women who are or may be pregnant (see 4.4. Special Warnings and Precautions during use. PRECAUTIONS, Pregnancy and Exposure to finasteride – danger to male fetus).

4.4 Special Warnings and Precautions during Use
PRECAUTIONS
FINASTERIDE MEVON 5MG TABLET is not indicated for use in children (see PRECAUTIONS for pediatric use), or in women (see EXPOSURE TO FINASTERIDE – DANGER FOR MALE FETUS and 4.6 Pregnancy and lactation).

EXPOSURE TO FINASTERIDE - DANGER FOR MALE FETUS
Women who are pregnant or may be pregnant should not contact fragmented or broken tablets of FINASTERIDE MEVON 5MG TABLET due to possibility of miscarriage due to finasteride and the subsequent danger for male fetus (see 4.6 Pregnancy and Lactation). The FINASTERIDE MEVON 5MG TABLET are coated and prevent contact with the active ingredient when they are used regularly, on condition that the tablets are not broken or fragmented.

PREGNANCY
FINASTERIDE MEVON 5MG TABLET is contraindicated for use in women who are or may be pregnant (see 4.3 Contraindications).
On account of the ability of the inhibitors of 5-a-reductase to metabolize testosterone into dihydrotestosterone (DHT), these active ingredients including finasteride may cause irregularities to a male fetus' external genitals, carried by a pregnant woman who received finasteride.

PRECAUTIONS
General
Patients with great urine residual or/ and strongly reduced urine flow rate should be controlled carefully for obstructive uropathy.

Breast cancer has been reported in men taking finasteride 5mg during clinical trials and 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.

The following additional adverse experiences have been reported in post-marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
Psychiatric disorders: suicidal ideation

Effect to PSA and control for cancer
No clinical benefit has appeared till now in patients with prostatic cancer treated with finasteride 5mg tablets. Patient with BPH (benign Prostatic Hyperplasia) and increased PSA were enrolled in controlled clinical studies with repeated PSA measurements and prostatic biopsies. In these studies finasteride 5mg tablet did not seem to alter the frequency of prostatic cancer appearance. The total frequency of prostatic cancer appearance was not significantly different in patients who were receiving treatment with finasteride 5mg tablet or placebo.

Rectal digital examination, and also other exams for prostatic cancer should be performed in patients with BPH before starting treatment with finasteride 5mg tablet and also periodically for detecting prostatic cancer.

In general a basic value for PSA>10ng/ml (Hybritech) presupposes further control and biopsy. For PSA levels between 4 and 10ng/ml,

further control is indicated. Significant over coverage exists between PSA values in men with and without prostatic cancer. For this reason in men with BPH, PSA values within normal values do not exclude prostatic cancer irregardless of the treatment with finasteride 5mg tablet. A value of PSA<4ng/ml does not exclude the existence of prostatic cancer.

Finasteride 5mg tablet reduces PSA levels in plasma approximately by 50% in patients with BPH even during the presence of prostatic cancer. This reduction of PSA levels in serum, in patients with BPH treated with finasteride 5mg tablet should be taken into account when evaluation of date for PSA is performed and does not exclude the simultaneous existence of prostatic cancer. This reduction is predictable for the whole spectrum of PSA values although it may vary in any patient separately. An analysis of PSA values from more than 3000 patients in a double-blind placebo controlled study of four years duration where the long-term efficacy and safety study (PROHYPE Long-term Efficacy and Safety Study, PLESS) certified that in usual patients treated with finasteride 5mg tablet for six months or more, the PSA values should be doubled in order to be compared with normal values in men who are not under medication. This adjustment maintains the sensitivity and specificity of PSA and preserves its ability to trace prostatic cancer. Any existing increase of PSA levels during treatment with finasteride 5mg tablet, should be carefully controlled.

Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride 5mg tablet. The ratio of free to total PSA remains constant even under the influence of finasteride 5mg tablet. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment to its value is necessary.

Drug/lab control of interactions
Effect on PSA levels
PSA concentrations in serum are correlated with patient's age and the prostatic size, and the prostatic size is correlated with the patient's age. During lab control of PSA levels, it should be taken into account the fact that PSA levels are reduced in patients who are under treatment with finasteride 5mg tablet. In most patients, a quick reduction of PSA is noted during the first months of treatment and then PSA levels are stabilized in a new value. This new value approaches half of the value before treatment.
For this reason in usual patients following treatment with finasteride 5mg tablet for six months or more, PSA values should be doubled in order to be compared with normal values in men who are not under treatment. For clinical interpretation see PRECAUTIONS, Effect on PSA and cancer control.

Pediatric Use
FINASTERIDE MEVON 5MG TABLET is contraindicated for use in children.
Its safety and efficacy is not documented in children.

4.5 Drug to drug interaction or other forms of interaction
No drug to drug interaction has been found that is of clinical significance. Finasteride 5mg tablet does not seem to affect significantly the cytochrome P450 (CYP) - the enzymatic system where drugs may interact during their metabolism. Drugs which have been studied in man have included propranolol, digoxin, glybouride, warfarin, theophylline and antipyrine without having found clinically important interactions.

Another simultaneous treatment
Despite that particular studies of interaction have not been made, finasteride 5mg tablet was used at the same time in clinical studies with ACE-inhibitors, inhibitors of the angiotensin-converting enzyme (ACE). Acetaminophen, acetylsalicylic acid, diuretics, inhibitors of calcium channels, cardiac nitrites, inhibitors of HMG-CoA reductase, non-steroid anti-inflammatory drugs, benzodiazepines, H2-antagonists and quinolones, have been co-administered without any clinically significant undesirable interactions.

4.6 Pregnancy and lactation
Use during pregnancy
(See CONTRAINDICATIONS)
FINASTERIDE MEVON 5MG TABLETS is not indicated for use by women.
Administration of finasteride in pregnant rats, in doses varied from 100µg/Kg/day up to 100mg/Kg/day (1-1000 times the recommended human dose) had resulted in a dose-dependant development of hypospadias in percentage of 3.6 to 100% of male offspring. Male offspring of pregnant rats were born with reduced weight of prostate and seminal vesicles, delay in separation of foreskin and temporary development of papilla after the administration of finasteride ≥30µg/Kg/daily (≥3/10 of the recommended human dose). The crucial period where these effects were observed on male rats was found to be the 16^{th} – 17^{th} day of pregnancy.

The alterations described are the expected pharmacological actions of drugs belonging to the category of inhibitors of 5alpha-reductase and are similar to those mentioned in male infants with genetic deficiency of 5alpha-reductase. We did not note any abnormality to female offspring exposed intrauterine to any dose of finasteride.

No abnormalities appearance is noted at the first parental generation (F1) of male or female offspring coming from copulation of male rats treated with finasteride (80mg/kg/daily, 61 times the human exposure) with female who had not been treated. Administration of 3mg/kg/daily of finasteride (30 times the recommended human dose) during the last period of pregnancy and lactation resulted in a slightly reduced fertility to male offspring of the first Medical generation F1. No abnormality was noted to female offspring. No case of malformation was noted to feti of rabbits exposed to finasteride intrauterine from the 16^{th} – 18^{th} day of pregnancy and in doses up to 100mg/kg/daily (1000 times from the recommended human dose). Anyway, effects on external male genitals should not be expected from the fact that the rabbits were not exposed to finasteride during the crucial period of development of genitals.
The effects from the exposure to finasteride intrauterine during fetal development were evaluated to small apes (days of pregnancy 20-100) a species more allied to man than rats and rabbits. The intravenous administration of finasteride to pregnant apes in doses of 800ng/day (at least 60-120 times the estimated amount in semen of a man who have taken 5mg finasteride, and to which a woman could be exposed via semen) did not cause abnormalities to male feti. In confirmation of the relation ape-model and of the development of human fetus, the administration of very high dose of finasteride per os (2mg/kg/day, 20 times the recommended dose to men or about 1-2 millions the estimated amount in semen) to pregnant apes led to genetic abnormalities of external genitals of male feti.

No other abnormalities were noted to male feti and also to female feti related to finasteride at any dosage whatsoever.

Nursing mothers
FINASTERIDE MEVON 5MG TABLETS is not indicated for use by women. It is not known if FINASTERIDE MEVON 5MG TABLETS is excreted to breast milk.

4.7 Influence on driving ability and machinery operation
FINASTERIDE MEVON 5MG TABLETS does not influence the ability to drive or operate machinery.

4.8 Side-effects
FINASTERIDE MEVON 5MG TABLETS is well tolerated in general. Its side-effects are mild and transient.

In PLESS study, 1524 patients following a treatment with 5mg daily and 1516 patients who were taking placebo, were evaluated as far as its safety is concerned for a period of time longer than 4 years. 4.9% (74 patients) interrupted the treatment due to side-effects connected with finasteride 5mg tablet in comparison with 3.3% (50 patients) who were taking placebo. 3.7% (57 patients) who were receiving medication with finasteride 5mg tablet and 2.1% (32 patients) who were receiving placebo interrupted the treatment as a result of side-effects related to sexual function and these were the most frequently reported side-effects.

The only clinically undesirable effects considered by researchers as potentially, possibly or definitely related to the medicine, for which the possibility of appearance with finasteride 5mg tablet was ≥1% and greater than placebo during the 4 years of study, were those related to sexual function, breast complaints and erythema. During the first year of study, impotence was reported to 8.1% of the patients who were taking finasteride 5mg tablet in comparison with the 3.7% of the patients who were taking placebo, reduced libido was reported at 6.4% in comparison with the 3.4% in placebo and disorders in ejaculation at 0.8% in comparison with 0.1% in placebo respectively. During the 2-4 years of the study there was no significant difference between the two groups of therapy as far as the percentages of appearance is concerned for the these three undesirable effects. The total percentages in years 2-4 were: incompetence, (5.1% for finasteride 5mg tablet vs 5.1% for placebo), reduced libido (2.6% vs 2.6%) and disorder in ejaculation (0.2% vs 0.1%). The first year, reduced volume of ejaculation was reported to percentages 3.7% and 0.8% of the patients under finasteride 5mg tablet and placebo respectively, in the years 2-4 the total percentage was 1.5% for finasteride 5mg tablet and 0.5% for placebo. In the first year increase of breasts (0.5% vs 0.1%), sensitivity to breasts (0.4% vs 0.1%) and rash (0.5% vs 0.2%) were also reported. In the years 2-4 the total percentages were, increase of breasts (1.8% vs 1.1%) sensitivity to breasts (0.7% vs 0.3%) and rash (0.5% vs 0.2%).

The profile of undesirable effects in placebo controlled studies of phase III with duration of 1 year; and at extensions of 5 years duration that were included 853 patients who were treated for 5-6 years, was similar with that reported in the years 2-4 in the study PLESS.

There are no elements of increase in the frequency of appearance of the undesirable effects with the increased duration of treatment with finasteride 5mg tablet. The frequency of appearance of new sexual undesirable effects related to the drug, are decreased with the continuation of the treatment.

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, of whom 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving finasteride 5mg tablet and 1147 (24.4%) men receiving placebo. In the finasteride group, 280 (6.4%) men had prostate cancer with Gleason scores of 7 – 10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Additional analyses suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride group may be explained by a detection bias due to the effect of finasteride on prostate volume. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2) at diagnosis. The relationship between long-term use of finasteride 5mg tablet and tumors with Gleason scores of 7 – 10 is unknown.

The following additional undesirable effects were reported after the marketing of the drug:
- Reactions of hypersensitivity including pruritus, urticaria and swelling of lips and face.
- Testicular pain
- Breast tenderness, breast enlargement and breast cancer. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia, or nipple discharge.
- Depression

Laboratory findings
When PSA's laboratory results are evaluated, attention should be paid to the fact that PSA levels are reduced in patients under treatment with finasteride 5mg tablet (see 4.4 Special warnings and Special Precautions, PRECAUTIONS).

No other difference in the usual laboratory parameters was not noted among patients under treatment with placebo or finasteride 5mg tablet.

4.9 Overdose
Patients were administered one dose of finasteride 5mg tablet up to 400mg and multiple doses of finasteride 5mg tablet up to 80mg/daily for three months, without any undesirable effects. No particular treatment is recommended in any possible overdose with finasteride 5mg tablet.

Significant mortality as noted in male and female mice in the administration of one dose per os of up to 1500mg/m^2 (500mg/kg) and in female and male rats in one per os dose of up to 2360 mg/m^2 (400mg/Kg), 5900 mg/m^2 (1000mg/Kg) respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CLINICAL PHARMACOLOGY
Benign Prostate Hyperplasia (BPH) has been presented in the majority of men above 50 years old and the frequency of the disease is increased with age. As ensues from epidemiological studies the increase of the size of the prostate gland is connected with 3 times bigger risk for acute retention of urine and operation of the prostate. Men with a prostate big in size are also 3 times more possible to have moderate to severe degree of urological symptoms or reduction in urinary flow rate in comparison with men having a smaller prostate.

The development and enlargement of the prostate gland and also the subsequent Benign Prostate Hyperplasia (BPH) is dependent on the androgen 5alpha dihydrotestosterone (DHT). Testosterone secreted by the testicles and the adrenal glands, is quickly metabolized into DHT by the enzyme 5 alpha-reductase initially at the prostate gland, liver and skin where is bounded afterwards in the nucleus of the cells

of these tissues.

Finasteride is a competitive and specific inhibitor of 5 alpha-reductase, by which a stable enzyme complex is progressively formed, whose disintegration is extremely slow (tl/2-30 days). In vivo and In vitro finasteride has showed that it is a specific inhibitor of type II of 5alpha-reductase and has no affinity with the androgens receptors.

One per os administration of a dose of finasteride 5mg, causes quick reduction in the concentration of DHT in plasma with the maximum result appearing 8 hours after the first dose. Since the levels of finasteride vary during the whole 24hrs, the levels of DHT remain stable during that period by showing that the concentrations of the drug in plasma are not related directly with the concentrations of DHT in plasma

In patients with Benign Prostate Hyperplasia (BHT), finasteride when administered for 4 years in a dose of 5mg/day showed that it reduces the concentrations of DHT in the circulation approximately by 70% and furthermore it was connected with an average reduction in the prostate volume by 20%. Moreover PSA was reduced by 50% from the initial values, showing in this way a reduction in the increase of the prostate epithelial cells. The repression of DHT and the involution to prostate hyperplasia together with the accompanying reduction in PSA levels were maintained in studies with duration up to 4 years. In these studies the levels of testosterone in the circulation were increased by 10-20% approximately, although they remained within normal limits.

When finasteride 5mg tablet was administered for 7-10 days to patients that were going to be subjected to prostatectomy, the drug caused reduction of endoprostatic DHT approximately by 80%. The endoprostatic concentration of testosterone was increased up to 10 times above the pre-treatment levels. In healthy volunteer men who were subjected to treatment with finasteride 5mg tablet for 14 days, the interruption of the treatment resulted to the rehabilitation of the levels of DHT in plasma to the pre-treatment levels within 2 weeks. In patients who were administered finasteride 5mg tablet for three months, the interruption of the treatment resulted to the rehabilitation of the prostate volume to the pre-treatment levels after three months approximately.

Finasteride had no effect compared to placebo within the framework of circulating cortisol, estradiol, prolactin, thyroid-stimulating hormone or thyroxin. There was also noted no significant effect in the lipids profile of plasma (e.g. total cholesterol, lipoproteins of low density, lipoproteins of high density and triglycerides) or in the mean osseous density. An increase was noted to 15% approximately of LH – Luteinizing hormone and 9% in FSH – Follicle Stimulating Hormone in patients who were been being administered treatment for 12 months, although these levels remained within normal limits. The response of LH and FSH on GnRH – Gonadotropin Releasing Hormone was not affected, a fact that shows that the control made by the axis pituitary gland — testicles is not affected.

A treatment with finasteride 5mg tablet for 24 weeks for the evaluation of the semen parameters, in healthy male volunteers, did not revoke influence on the total volume of ejaculation, on the semen mobility, its morphology or its PH. A mean reduction by 0.6ml was noted on the volume of ejaculation with simultaneous reduction on the total semen per ejaculation. These parameters remained within normal limits and were reversible on the interruption of the drug.

Finasteride appeared to inhibit the metabolism of C19 and also of C21 steroids and since then it appeared to have inhibit effect both on the hepatic and the peripheral activity of 5a-reductase of type II. The DHT metabolites in the serum, glycuronide, androstenediol and glycuronide of androsterone were also reduced.

This metabolic model is similar to that noted in persons with genetic abnormality in 5alpha-reductase of type II, who were having significantly decreased levels of DHT and prostates of small volume who were not presenting Benign Prostate Hyperplasia (BPH). These persons were having urogenital abnormalities at birth and biochemical abnormalities, but they had no other clinically significant disorders, as consequence of the deficit of 5alpha-reductase of type II.

Clinical Studies
The particulars form the studies described below, show reduced risk for acute retention of urine and surgical improvement of the symptoms connected with BPH, increase of the maximum urinary flow rate and reduction in prostate size, which suggest that finasteride 5mg tablet converts the development of BPH in patients with an enlarged prostate.

Finasteride 5mg tablet at 5mg/day was initially evaluated in patients with symptoms of BPH and ascertained enlarged prostate by digital exam, in two randomized, placebo controlled, double-blind studies, with duration of one year and at their open extension with duration of 5 years. Out of 536 patients having been initially randomized in taking finasteride 5mg tablet 5mg/day, 234 completed the additional period of treatment of 5 years and were possible to be evaluated. The parameters of effectiveness were the grade of the symptoms, the maximum urinary flow rate and the prostate size.

Finasteride 5mg tablet was further evaluated in the finasteride 5mg tablet Long-term Efficacy and Safety Study, PLESS, a double-blind randomized controlled by placebo multicentric study with duration of 4 years. In this study the influence of the treatment with finasteride 5mg tablet of 5mg/day in the symptoms of BPH was evaluated and in the urological facts connected with BPH [surgical intervention (e.g. transurethral prostate excision and prostatectomy) or acute retention of urine that requires catheterization]. 3040 patients aged from 45 to 78 years old with moderate up to severe symptoms of BPH and enlarged prostate ascertained by digital exam were randomized in the study (1524 in finasteride group and 1516 in placebo group) and 3016 patients were evaluated as far as efficacy is concerned. 1883 patients completed the 4 years study (1000 in the finasteride group and 883 in the placebo group). The maximum urinary flow rate and the prostate size were also evaluated.

EFFECT ON ACUTE RETENTION OF URINE AND ON THE NEED FOR SURGICAL PROCEDURE
In the 4 years study PLESS, surgical procedures and acute retention of urine that required catheterization occurred on 13.2% of the patients who were taking finasteride 5mg tablet, a fact that shows 51% reduction in the risk for surgical procedure or acute retention of urine in a period of time of 4 years. The finasteride 5mg tablet reduced the risk for surgical procedures by 55% (10.1% for placebo in comparison with 4.6% for finasteride 5mg tablet) and reduced the risk for acute retention of urine by 57% (6.6% for placebo in comparison with 2.8% for finasteride 5mg tablet). The reduction of risk was apparent among the groups of treatment at the first evaluation (4 months) and was maintained during all 4 years of the study. The following table shows the appearance rates and the reduction in the risk of urological events during the study.

Table 1 RATES OF APPEARANCE OF UROLOGICAL EVENTS AND REDUCTION OF THE RISK BY FINASTERIDE 5MG TABLET IN

A PERIOD OF 4 YEARS

Urological events	Percentage of Patients		
	Placebo (r=1503)	Finasteride 5mg (n=1513)	Reduction of risk
Surgical Procedure or Acute Retention of Urine	13.2%	6.6%	51%*
Surgical Procedure + TURP	10.1% 8.3%	4.6% 4.2%	55%* 49%*
Acute Retention of Urine	6.6%	2.8%	57%

+ Surgical Procedure related to BPH
* p<0.001

EFFECT ON GRADING THE SYMPTOMS

In the two studies of phase III, with duration of 1 year, the average grading of the symptoms was decreased from baseline as early as week 2. In comparison with placebo we noted in these studies, a significant improvement in the symptoms by months 7 and 10. Even if in some patients an early improvement was noted on the urological symptoms, a study of treatment of 6 months at minimum was in general necessary in order to be evaluated if a satisfactory result has been achieved as far as the relieve of the symptoms is concerned. The improvement in the BPH symptoms was maintained during the first year and during the additional 5 years of the extension of the studies.

The patients in PLESS study of the 4 years had symptoms of moderate to severe degree at the beginning (average grade approximately 15 marks in a grading scale from 0-34 marks) In patients who remained under treatment for the whole duration of the 4 years of the study, finasteride 5mg tablet improved the grading of the symptoms by 3.3 grades in comparison with the 1.3 grades in placebo group (p<0.001).

The improvement in the symptoms grading was apparent during the first year in the patients treated by finasteride 5mg tablet and that improvement was continued up to the fourth year. Improvement in the grading of the symptoms was in the first year as compared to patients who were taking placebo, the symptoms were aggravated in the first year. The patients with symptoms of moderate up to severe degree prior to the beginning of the treatment seem to have the best improvement in the grading of the symptoms.

EFFECT ON THE MAXIMUM URINARY FLOW RATE

In two studies of Phase III with duration of 1 year, the maximum urinary flow rate by week 2 was significantly increased in comparison with the initial one. In comparison with placebo a significant increase in the maximum urinary flow rate was noted in these studies by months 4 and 7. This result was maintained during the first year and during the 5 additional years of extension of these studies.

In the study PLESS of 4 years duration, a clear separation existed by month 4 between the groups of treatment in terms of the maximum urinary flow rate in favour of finasteride 5mg tablet and this difference was observed throughout the study. The average value of the maximum urinary flow rate prior to the beginning of the study was 11mL/sec approximately and in both groups of treatment. In the patients who remained under treatment during the study and had evaluable urinary flow rate, finasteride 5mg tablet increased the maximum urinary flow rate by 1.9mL/sec in comparison with 0.2mL/sec in placebo group.

EFFECT ON PROSTATE SIZE

In two studies of phase III of 1 year duration, the average prostate size prior to the beginning of the study varied between 40-50cc. In both studies the prostate size reduced significantly in comparison both with the initial values both with placebo during first evaluation (3rd month of the study). That result was maintained during the first year and during the additional 5 years of the extension of the studies.

In the study PLESS of 4 years duration, an annual evaluation of the prostate size was being performed by a magnetic resonance imaging tomographer in a sub-group of patients (n=284). In patients under treatment with finasteride 5mg tablet the prostate size was reduced in comparison both with the initial values and with placebo during the 4 years of the study. From the patients of the sub-group of the magnetic resonance imaging who remained under treatment during the whole study, finasteride 5mg tablet reduced the prostate size by 17.9% (from initial 55.9cc to 45.8cc at the, end of 4 years) in comparison with an increase by 14.1% (from 51.3 cc to 58.5 cc) in the group of placebo (p<0.001).

PROSTATE SIZE AS A PREDICTION FACTOR OF THERAPEUTIC RESPONSE

One meta-analysis where data of 1 year was combined from seven double-blind, controlled by placebo studies of similar design, where 4491 patients with symptomatic BPH were included, showed that for patients under treatment with finasteride 5mg tablet, the degree of improvement of the symptoms and of the maximum urinary flow rate was bigger in patients with an enlarged prostate (approximately 40cc and larger) prior to the beginning of the treatment.

ADDITIONAL CLINICAL STUDIES

The urodynamic effects of finasteride in the treatment of the obstruction of the urinary bladder due to BPH, were evaluated by interventional techniques in one double-blind, placebo controlled study of 24 weeks in 36 patients with moderate or degree grade symptoms of urine obstruction and with maximum urinary flow rate less than 15ml/sec. Significant improvement of the obstruction that was expressed by the significant improvement of the pressure of detrusor muscle and the increase of the average urinary flow rate, was noted in comparison with placebo, in patient who were taking 5mg of finasteride 5mg tablet.

The effect of finasteride on the volume of the peripheral and periurethral zone of the prostate was evaluated by a magnetic resonance imaging tomographer in 20 men with BPH, in a double-blind, controlled by placebo study, of one year duration.

The patients who were taking finasteride 5mg tablet in contrast with those who were taking placebo, presented significant reduction [11.5 3.2cc(SE)] of the total size of the gland. That reduction was attributed mainly to the reduction (6.2 ± 3cc) of the volume of the periurethral zone.

Since the periurethral zone is responsible for outflow obstruction, this reduction may account for the beneficial clinical response observed in these patients.

5.2 Pharmacokinetic properties
Following the oral administration of radio-detected by $_{14}$C finasteride to man, a percentage of 39% in average (variation 32-46%) of the dose was secreted to urine in the form of metabolites 57% (variation 51-64%) was secreted to faeces.

In this study, two metabolites of finasteride were detected which are responsible for a small only part of the inhibiting action of finasteride to 5alpha-reductase.

In relation to an intravenous administration of a reference dose or the oral bioavailability of finasteride is approximately 80%. Bioavailability is not affected by food. The maximum concentration of finasteride in plasma was achieved 2 hours after the administration of one dose and the absorption was complete after 6 to 8 hours. The average time of half-life in plasma is 6 hours. The protein binding is 93%. The plasma clearance and the distribution volume of finasteride was approximately 165mL/min and 76 liters respectively.

One multiple-dose study showed a slow accumulation of small amounts of finasteride as time passes by. Following a daily dosage of 5mg/day trough plasma concentration of finasteride of about 8-10ng/mL were reached and remained stable as time passes by.

The rate of excretion of finasteride is reduced in some degree in old people. The average half-life of finasteride was elongated from 6 hours in men aged 18-60 years old, to 8 hours in men aged above 70 years old.

This finding was not clinically significant and therefore no decrease of dosage is required.

In patients with chronic renal impairment with creatinine clearances ranging from 9 to 55 mL/minute, area under the curve (AUC), maximum plasma concentrations, half-life and protein binding of unchanged finasteride after a single dose of ^{14}C-finasteride were similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in faecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in BPH patients with normal renal function receiving up to 80mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater. Therefore it is not necessary to adjust dosage in patient with renal insufficiency who are not dialysed, as the therapeutic window of finasteride is adequate and as a correlation between creatinine clearance and accumulation could not be demonstrated.

Finasteride has been traced in the cerebrospinal fluid of patients who were taking finasteride for a period of 7-10 days, but the drug does not seem to be gathered selectively in the cerebrospinal fluid. Finasteride was also traced in the seminal fluid of people who were taking finasteride 5mg tablet at a dosage of 5mg/day. The amount of finasteride in the seminal fluid was 50 to 100 times less than the dose of finasteride (5µg) and had no effect on the circulating levels of DHT of adult men (see also 5.3 Pre-clinical safety particulars).

5.3 Pre-clinical safety particulars
Carcinogenesis, mutagenic action, influence on fertility
No oncogenic action was noted in a 24-month study on rats, who were taking finasteride doses up to 160mg daily the male ones and 320 mg daily the female ones. These doses caused systematic exposure to rats 111 and 274 times from these noted in men who were taking the recommended human dose of 5mg daily. All the measurements of the report were based on the calculation of AUC (0-24h) for animals and the average value of AUC (0-24h) for man (0.4mg.hr/ml).

In a 19-month study of carcinogenesis, in CD-1 mice, we noted one statistically significant increase ($p \leq 0.05$) in the appearance of adenoma in Leydig's cells, with one dose of 250mg/Kg/daily (228 times the human exposure). In mice, with one dose of 25mg/kg/daily (23 times the human exposure) and in rats with one dose ≥40mg/kg/daily (39 times the human exposure) we noted increase of the frequency of hyperplasia of Leydig's cells. A positive correlation has been proved between hyperplastic alterations of Leydig's cells and the increase in plasma LH levels (2-3 times above control) in both kinds of rodents who were treated with high doses of finasteride. No changes were noted in Leydig's cells that were related to the drug neither in rats or in dogs treated with finasteride for one year, with doses of 20mg/kg/day and 45mg/kg/day (30 and 350 times respectively the human exposure) or in mice which were treated for 19 months with a dose of 25mg/kg/day (2-3 times the human exposure). No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In one in vitro test of chromosomal aberrations where ovarian cells from Chinese hamsters were exposed to high concentrations 450-550ml/µmol/finasteride, a slight increase of chromosomal aberrations occurred. These concentrations correspond to 4000-5000 times the maximum levels in plasma in human when he/she is administered a total dose of 5mg. Further, the concentrations (450-500µmol) used in *in vitro* studies are not achievable in a biological system. In one *in vitro* study of chromosomal aberration in mice, we noted no increase in the chromosomal aberration related with the drug, with finasteride in the maximum tolerable dose of 250mg/kg/day (228 times the recommended human dose, as determined in the studies of carcinogenesis).

Studies of reproduction
In sexually mature male rabbits, which were administered finasteride 80mg/kg/day (543 times the human exposure) for 12 weeks no influence on their fertility, the quantity of semen or the volume of ejaculation was noted. In sexually mature male rats, which were administered finasteride 80mg/kg/day (61 times the human exposure) there were no significant influences on their fertility following 6 or 12 weeks of treatment. However when treatment was continued for more than 24 up to 30 weeks an apparent decrease in fertility and insemination was noted, and a significant reduction in the weight of seminal vesicles and of prostate. All these influences were reversible within 6 weeks after the interruption of the treatment. Undesirable influence on testicles or on the procedure of coupling related to the drug did not appear both in rats and rabbits as well.
This decrease of fertility in rats, which were administered finasteride, is secondary due to the influence of finasteride on auxiliary genital organs (prostate and seminal vesicles), with resulting inability to form a seminal embolus. The spermatic embolus is essential for the normal fertility of rats and has no relation with man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Active ingredient:

Finasteride

Excipients:
Microcrystalline cellulose 102, Pregelatinized maize starch 1500, Sodium starch glycolate, Iron oxide yellow, Sodium docusate, Magnesium stearate

Coating:
Opadry blue (02H0569)

6.2 Incompatibilities
None known.

6.3 Life duration
36 months

6.4 Special precautions for the product's storage
Storage and handling
Store it in room temperature at or below 30°C (86°F). If the film of coating of the tablets of FINASTERIDE MEVON 5MG TABLETS has been broken (e.g. is fragmented), the tablets should not be contacted by a woman who is pregnant or could be pregnant due to the possibility of miscarriage due to finasteride and the subsequent danger for male fetus (see 4.4 Special Warnings and Precautions during Use, WARNINGS, EXPOSURE TO FINASTERIDE – RISK FOR MALE FETUS and 4.6 Pregnancy and Lactation, Pregnancy).

6.5 Nature and components of the container
PVC/PE/PVDC/Aluminium blister
Pack sizes: 30, 50, 100 tablets
Not all pack sizes may be marketed in Singapore.

6.6 Directions for use
There are no special instructions. Take one tablet of FINASTERIDE MEVON 5MG TABLET daily, with or without food.

6.7 Holder of the License of Marketing
Novem Pharma Pte Ltd
23 New Industrial Road
#03-08 Solstice Business Center
Singapore 536209

7. NUMBER OF LICENSE OF MARKETING
SIN13681P

8. DATE OF REVISION OF THE TEXT
Nov 2021