Public Assessment Report

Decentralised

Finiol 5mg Film-coated Tablets
Nikitid 5mg Film-coated Tablets
Finasteride 5mg Film-coated Tablets

Finasteride

UK/H/1466/01/DC
UK/H/1467/01/DC
UK/H/1468/01/DC

Pharmathen Pharmaceuticals S.A.
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# Module 1

| **Product Name** | Finiol 5mg Film-coated Tablets  
|                 | Nikitid 5mg Film-coated Tablets  
|                 | Finasteride 5mg film coated tablets |
| **Type of Application** | Standard Abridged Decentralised (Article 10.1) |
| **Active Substance (INN)** | Finasteride |
| **Pharmacotherapeutic Classification (ATC)** | Alpha-adrenoreceptor antagonists  
|                 | ATC code G04C  Group A02 |
| **Pharmaceutical Form and Strength** | Film coated tablets, 5mg |
| **Procedure Numbers** | UK/H/1466/01/DC  
|                 | UK/H/1467/01/DC  
|                 | UK/H/1468/01/DC |
| **RMS** | UK |
| **CMS** | UK/H/1466-01-DC: EE, EL, IS, IT, LT, LV  
|                 | UK/H/1467-01-DC: IT  
|                 | UK/H/1468-01-DC: IT |
| **Start Date** | 09/06/2008 |
| **End Date** | 24/07/2009 |
| **MA Number** | PL 17277/0018-20 |
| **Name and address of MA holder** | Pharmathen S.A.,  
|                 | 6 Dervenakion str., 15351 Pallini, Attiki, Greece |
Module 2
Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Finiol 5mg film – coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of finasteride
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Round, biconvex, blue film – coated tablets, with no defect on coating layer, scored on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Finiol is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:
– cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH
– reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Finiol 5 mg tablets should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).
4.2 **Posology and method of administration**
The recommended adult dose is one 5 mg tablet daily, with or without food.

Finiol can be administered alone or in combination with the alpha-blocker doxazosin.

Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.

*Renal insufficiency*
No dosage adjustment is required in patients with varying degrees of renal insufficiency (creatinine clearance as low as 9 ml/minute).

*Use in the elderly*
No dosage adjustment is required in the elderly.

*Hepatic insufficiency*
There are no data available in patients with hepatic insufficiency.

*Use in children*
Finiol is contra-indicated in children (see section 4.3).

4.3 **Contraindications**
Hypersensitivity to the active substance or to any of the excipients.
Women who are or may potentially be pregnant.
Children.

4.4 **Special warnings and precautions for use**
*General*
Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.

*Effects on prostate-specific antigen (PSA) and prostate cancer detection*
No clinical benefit has yet been demonstrated in patients with prostate cancer treated with Finiol.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with Finiol and periodically thereafter.
Generally, when PSA assays are performed a baseline PSA > 10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with Finiol. A baseline PSA < 4 ng/ml does not exclude prostate cancer.

Finiol causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with Finiol should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with Finiol 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 increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to therapy with Finiol.

Percent free PSA (free to total PSA ratio) is not significantly decreased by Finiol and remains constant even under the influence of Finiol. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.

Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with finasteride.

There is no experience in patients with liver insufficiency. Since finasteride is metabolised in the liver caution is advised in patients with decreased hepatic function as the plasma-levels of finasteride may be increased in such patients.

**4.5 Interaction with other medicinal products and other forms of interaction**

No clinically important drug interactions have been identified. Finiol does not appear to significantly affect the cytochrome P450 - linked drug metabolising enzyme system.

Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

*Other concomitant therapy*

Although specific interaction studies were not performed in clinical studies, Finiol was used concomitantly with ACE inhibitors, alpha-blockers, beta - blockers, calcium channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG – CoA reductase inhibitors, non - steroidal anti - inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.
4.6 Pregnancy and lactation

Pregnancy

Finiol is contra-indicated in women who are or may potentially be pregnant (see section 4.3).

Because of the ability of Type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

Studies in animals have shown reproductive toxicity (see section 5.3).

Exposure to finasteride – risk to male foetus

Women should not handle crushed or broken tablets of Finiol when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see 'Pregnancy'). Finiol tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Small amounts of finasteride have been recovered from the semen in subjects receiving Finiol 5 mg/day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue Finiol.

Lactation

Finiol is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

4.7 Effects on ability to drive and use machines

Finiol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been reported during the clinical studies and/ or in post marketing experience.

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</tr>
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</table>

Pharmathen, Finiol 5mg/Nikitid 5mg/Finasteride 5mg Film-coated Tablets
| Site conditions | | | the face and lips |
|-----------------|----------------|-------------------|
| Immune system disorders | | | hypersensitivity reactions, including pruritus, urticaria |
| Psychiatric disorders | decreased libido | | |
| Reproductive system and breast disorders | decreased volume of ejaculate, impotence | ejaculation disorder, breast enlargement, breast tenderness | testicular pain, breast secretion, breast nodules that were surgically removed in single patients |
| Skin and subcutaneous tissue disorders | rash | | |

There was no evidence of increased adverse experiences with increased duration of treatment with Finiol and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

**Medical therapy of prostatic symptoms (MTOPS)**

The MTOPS study compared finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%.

**Other long-term data**

In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving Finasteride and 1147 (24.4%) men receiving placebo. In the Finasteride group, 280 (6.4%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%). Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of Finasteride and tumours with Gleason scores of 7-10 is unknown.

**Laboratory test findings**

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with Finiol. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with Finiol...
for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men.

For clinical interpretation see section 4.4, *Effects on prostate-specific antigen (PSA) and prostate cancer detection.*

No other difference was observed in patients treated with placebo or Finiol in standard laboratory tests.

### 4.9 Overdose

No specific treatment of overdosage with Finiol is recommended. Patients have received single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for up to three months without any adverse effects.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Testosterone-5α - reductase inhibitors

ATC code: G04CB01

Finasteride is a competitive inhibitor of human 5 α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Finiol is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

In clinical studies of patients with moderate to severe symptoms of BPH, an enlarged prostate on digital rectal examination and low residual urinary volumes, Finasteride reduced the incidence of acute retention of urine from 7/100 to 3/100 over four years and the need for surgery (TURP or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA symptom score (range 0-34), a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

*Medical therapy of prostatic symptoms (MTOPS)*

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34(p=0.002), 39 (p<0.001),
and 67% (p<0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67 (p=0.011), 31 (p=0.296), and 79% (p=0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.

* Titrated from 1 mg to 4 or 8 mg as tolerated over a 3-week period.

5.2 **Pharmacokinetic properties**

After an oral dose of ¹⁴C – finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine), and 57% of total dose was excreted in the faeces. Two metabolites have been identified which possess only a small fraction of the Type II 5α-reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6 – 8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately six hours in men aged 18 – 60 years to eight hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

In patients with chronic renal impairment, whose creatinine clearance ranged from 9 – 55 ml/min, the disposition of a single dose of ¹⁴C – finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. Dosage adjustment in non – dialysed patients with renal impairment is not necessary.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood – brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

5.3 **Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the
primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated amount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose.”

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Pregelatinized Maize Starch
Sodium starch glycollate
Iron oxide yellow (E172)
Sodium docusate
Magnesium stearate

Film-coating:
Hypromellose
Titanium Dioxide (E171)
Talc
Propylene Glycol
Indigo Carmine (E132)
Quinoline Yellow FCF (E104)
Sunset Yellow FCF (E110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PE/PVDC/Aluminium blister packs containing 15 or 30 or 100 film – coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Women should not handle crushed or broken Finiol tablets when they are or may potentially be pregnant (see 'Contra-indications, 'Pregnancy and lactation', Exposure to finasteride - risk to male foetus).

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

7 MARKETING AUTHORISATION HOLDER
Pharmathen S.A., 6 Dervenakion str. 153 51 - Pallini Attiki, Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/08/2009

10 DATE OF REVISION OF THE TEXT
20/08/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nikitid 5mg film – coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of finasteride
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Round, biconvex, blue film – coated tablets, with no defect on coating layer, scored on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Nikitid is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:
− cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH
− reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Nikitid 5 mg tablets should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).

4.2 Posology and method of administration
The recommended adult dose is one 5 mg tablet daily, with or without food.

Nikitid can be administered alone or in combination with the alpha-blocker doxazosin.
Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.

Renal insufficiency
No dosage adjustment is required in patients with varying degrees of renal insufficiency (creatinine clearance as low as 9 ml/min).

Use in the elderly
No dosage adjustment is required in the elderly.

Hepatic insufficiency
There are no data available in patients with hepatic insufficiency.

Use in children
Nikitid is contra-indicated in children (see section 4.3).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Women who are or may potentially be pregnant.
Children.

4.4 Special warnings and precautions for use
General
Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.

Effects on prostate-specific antigen (PSA) and prostate cancer detection
No clinical benefit has yet been demonstrated in patients with prostate cancer treated with Nikitid.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with Nikitid and periodically thereafter. Generally, when PSA assays are performed a baseline PSA >10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with Nikitid. A baseline PSA <4 ng/ml does not exclude prostate cancer.
Nikitid causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with Nikitid should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with Nikitid 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 increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to therapy with Nikitid.

Percent free PSA (free to total PSA ratio) is not significantly decreased by Nikitid and remains constant even under the influence of Nikitid. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.

Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with finasteride.

There is no experience in patients with liver insufficiency. Since finasteride is metabolised in the liver caution is advised in patients with decreased hepatic function as the plasma-levels of finasteride may be increased in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically important drug interactions have been identified. Nikitid does not appear to significantly affect the cytochrome P450 - linked drug metabolising enzyme system.

Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

Other concomitant therapy

Although specific interaction studies were not performed in clinical studies, Nikitid was used concomitantly with ACE inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG – CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy

Nikitid is contra-indicated in women who are or may potentially be pregnant (see section 4.3).

Because of the ability of Type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.
Studies in animals have shown reproductive toxicity (see section 5.3).

*Exposure to finasteride – risk to male foetus*

Women should not handle crushed or broken tablets of Nikitid when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see 'Pregnancy'). Nikitid tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Small amounts of finasteride have been recovered from the semen in subjects receiving Nikitid 5 mg/day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue Nikitid.

*Lactation*

Nikitid is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

### 4.7 Effects on ability to drive and use machines

Nikitid has no influence on the ability to drive and use machines.

### 4.8 Undesirable effects

The following undesirable effects have been reported during the clinical studies and/or in post marketing experience.

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<td>Psychiatric disorders</td>
<td>decreased libido</td>
<td>Reproductive system and breast disorders</td>
<td>decreased volume of ejaculate, impotence</td>
<td>ejaculation disorder, breast enlargement, breast tenderness</td>
<td>testicular pain</td>
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<td>----------------------------------------------------------</td>
<td>----------------</td>
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<td>Skin and subcutaneous tissue disorders</td>
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There was no evidence of increased adverse experiences with increased duration of treatment with Nikitid and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

*Medical therapy of prostatic symptoms (MTOPS)*

The MTOPS study compared finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%.

*Other long-term data*

In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving Finasteride and 1147 (24.4%) men receiving placebo. In the Finasteride group, 280 (6.4%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%). Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of Finasteride and tumours with Gleason scores of 7-10 is unknown.

*Laboratory test findings*

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with Nikitid. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with Nikitid for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men.

For clinical interpretation see section 4.4, *Effects on prostate-specific antigen (PSA) and prostate cancer detection.*
No other difference was observed in patients treated with placebo or Nikitid in standard laboratory tests.

4.9 Overdose
No specific treatment of overdosage with Nikitid is recommended.

Patients have received single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for up to three months without any adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Testosterone-5α-reductase inhibitors
ATC code: G04CB01

Finasteride is a competitive inhibitor of human 5α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Nikitid is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

In clinical studies of patients with moderate to severe symptoms of BPH, an enlarged prostate on digital rectal examination and low residual urinary volumes, Finasteride reduced the incidence of acute retention of urine from 7/100 to 3/100 over four years and the need for surgery (TURP or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA symptom score (range 0-34), a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

Medical therapy of prostatic symptoms (MTOPS)

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34(p=0.002), 39 (p<0.001), and 67% (p<0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67(p=0.011), 31 (p=0.296), and 79% (p=0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.
5.2 Pharmacokinetic properties
After an oral dose of \(^{14}\text{C}\) – finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine), and 57% of total dose was excreted in the faeces. Two metabolites have been identified which possess only a small fraction of the Type II 5\(\alpha\)-reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6 – 8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half – life of approximately six hours in men aged 18 – 60 years to eight hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

In patients with chronic renal impairment, whose creatinine clearance ranged from 9 – 55 ml/min, the disposition of a single dose of \(^{14}\text{C}\) – finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. Dosage adjustment in non – dialysed patients with renal impairment is not necessary.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood – brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg
finasteride, and to which a woman could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated amount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose.”

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Microcrystalline cellulose
Pregelatinized Maize Starch
Sodium starch glycollate
Iron oxide yellow (E172)
Sodium docusate
Magnesium stearate

Film-coating:
Hypromellose
Titanium Dioxide (E171)
Talc
Propylene Glycol
Indigo Carmine (E132)
Quinoline Yellow FCF (E104)
Sunset Yellow FCF (E110).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
PVC/PE/PVDC/Aluminium blister packs containing 15 film – coated tablets.

6.6 Special precautions for disposal
Women should not handle crushed or broken Nikitid tablets when they are or may potentially be pregnant (see 'Contra-indications, 'Pregnancy and lactation', Exposure to finasteride - risk to male foetus).

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

7 MARKETING AUTHORISATION HOLDER
Pharmathen S.A., 6 Dervenakion str. 153 51 - Pallini Attiki, Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/08/2009

10 DATE OF REVISION OF THE TEXT
20/08/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Finasteride 5mg film – coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of finasteride
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Round, biconvex, blue film – coated tablets, with no defect on coating layer, scored on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Finasteride is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:
− cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH
− reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Finasteride 5 mg tablets should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).

4.2 Posology and method of administration
The recommended adult dose is one 5 mg tablet daily, with or without food.

Finasteride can be administered alone or in combination with the alpha-blocker doxazosin.

Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.
Renal insufficiency
No dosage adjustment is required in patients with varying degrees of renal insufficiency (creatinine clearance as low as 9 ml/min).

Use in the elderly
No dosage adjustment is required in the elderly.

Hepatic insufficiency
There are no data available in patients with hepatic insufficiency.

Use in children
Finasteride is contra-indicated in children (see section 4.3).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Women who are or may potentially be pregnant.
Children.

4.4 Special warnings and precautions for use
General
Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.

Effects on prostate-specific antigen (PSA) and prostate cancer detection
No clinical benefit has yet been demonstrated in patients with prostate cancer treated with Finasteride.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with Finasteride and periodically thereafter. Generally, when PSA assays are performed a baseline PSA>10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with Finasteride. A baseline PSA <4 ng/ml does not exclude prostate cancer.

Finasteride causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with Finasteride should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with Finasteride 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 increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to therapy with Finasteride.

Percent free PSA (free to total PSA ratio) is not significantly decreased by Finasteride and remains constant even under the influence of Finasteride. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.

Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with finasteride.

There is no experience in patients with liver insufficiency. Since finasteride is metabolised in the liver caution is advised in patients with decreased hepatic function as the plasma-levels of finasteride may be increased in such patients.

4.5 Interaction with other medicinal products and other forms of interaction
No clinically important drug interactions have been identified. Finasteride does not appear to significantly affect the cytochrome P450 - linked drug metabolising enzyme system.
Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

Other concomitant therapy
Although specific interaction studies were not performed in clinical studies, Finasteride was used concomitantly with ACE inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMG – CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy
Finasteride is contra-indicated in women who are or may potentially be pregnant (see section 4.3).
Because of the ability of Type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

Studies in animals have shown reproductive toxicity (see section 5.3).

Exposure to finasteride – risk to male foetus
Women should not handle crushed or broken tablets of Finasteride when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see 'Pregnancy'). Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Small amounts of finasteride have been recovered from the semen in subjects receiving Finasteride 5 mg/day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue Finasteride.

Lactation
Finasteride is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

4.7 Effects on ability to drive and use machines
Finasteride has no influence on the ability to drive and use machines.

4.8 Undesirable effects
The following undesirable effects have been reported during the clinical studies and/or in post marketing experience.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
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<td></td>
<td>hypersensitivity reactions such as swelling of the face and lips</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hypersensitivity reactions, including pruritus, urticaria</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>decreased libido</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>decreased volume of ejaculate, impotence</td>
<td>ejaculation disorder, breast enlargement,</td>
<td>testicular pain</td>
<td>breast secretion, breast nodules that</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>breast tenderness</td>
<td>were surgically removed in single patients</td>
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</table>

There was no evidence of increased adverse experiences with increased duration of treatment with Finasteride and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

**Medical therapy of prostatic symptoms (MTOPS)**

The MTOPS study compared finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%.

**Other long-term data**

In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving Finasteride and 1147 (24.4%) men receiving placebo. In the Finasteride group, 280 (6.4%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%). Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of Finasteride and tumours with Gleason scores of 7-10 is unknown.

**Laboratory test findings**

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with Finasteride. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with Finasteride for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men.

For clinical interpretation see section 4.4, Effects on prostate-specific antigen (PSA) and prostate cancer detection.

No other difference was observed in patients treated with placebo or Finasteride in standard laboratory tests.

### 4.9 Overdose

No specific treatment of overdosage with Finasteride is recommended.
Patients have received single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for up to three months without any adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Testosterone-5α - reductase inhibitors
ATC code: G04CB01

Finasteride is a competitive inhibitor of human 5α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Finasteride is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

In clinical studies of patients with moderate to severe symptoms of BPH, an enlarged prostate on digital rectal examination and low residual urinary volumes, Finasteride reduced the incidence of acute retention of urine from 7/100 to 3/100 over four years and the need for surgery (TURP or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA symptom score (range 0-34), a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

Medical therapy of prostatic symptoms (MTOPS)

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34 (p=0.002), 39 (p<0.001), and 67% (p=0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34 (p=0.002), 39 (p<0.001), and 67% (p=0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67 (p=0.011), 31 (p=0.296), and 79% (p=0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.

* Titrated from 1 mg to 4 or 8 mg as tolerated over a 3-week period.
5.2 Pharmacokinetic properties
After an oral dose of $^{14}$C–finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine), and 57% of total dose was excreted in the faeces. Two metabolites have been identified which possess only a small fraction of the Type II 5α-reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6–8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately six hours in men aged 18–60 years to eight hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

In patients with chronic renal impairment, whose creatinine clearance ranged from 9–55 ml/min, the disposition of a single dose of $^{14}$C–finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. Dosage adjustment in non-dialysed patients with renal impairment is not necessary.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood–brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, feminisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x)
than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated amount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose.”

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Microcrystalline cellulose
- Pregelatinized Maize Starch
- Sodium starch glycollate
- Iron oxide yellow (E172)
- Sodium docusate
- Magnesium stearate

Film-coating:
- Hypromellose
- Titanium Dioxide (E171)
- Talc
- Propylene Glycol
- Indigo Carmine (E132)
- Quinoline Yellow FCF (E104)
- Sunset Yellow FCF (E110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister packs containing 15 film – coated tablets.
6.6 Special precautions for disposal
Women should not handle crushed or broken Finasteride tablets when they are or may potentially be pregnant (see 'Contra-indications, 'Pregnancy and lactation', Exposure to finasteride - risk to male foetus).

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

7 MARKETING AUTHORISATION HOLDER
Pharmathen S.A., 6 Dervenakion str. 153 51 - Pallini Attiki, Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/08/2009

10 DATE OF REVISION OF THE TEXT
20/08/2009
Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Finisol 5 mg film - coated tablet:
Finasteride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Finisol is and what it is used for
2. Before you take Finisol
3. How to take Finisol
4. Possible side effects
5. How to store Finisol
6. Further information

1. WHAT FINISOL IS AND WHAT IT IS USED FOR

Finisol belongs to a group of medicines called 5-alpha reductase inhibitors. It works by shrinking the enlarged prostate gland in men.

Your doctor has prescribed Finisol for you because you have a condition known as benign prostatic hyperplasia or BPH. Your prostate gland, which is near your bladder, has become bigger and is making it more difficult for you to pass urine.

Finisol helps to shrink the enlarged prostate and relieves your symptoms. Finisol will help reduce the risk of you developing a sudden inability to pass urine (known as acute urinary retention) and the need for surgery.

2. BEFORE YOU TAKE FINISOL

Finisol is for use in men only.

Do not take Finisol:
- if you are allergic (hypersensitive) to finasteride or any of the other ingredients of Finisol
- if you are a woman or a child (the condition for which Finisol is prescribed occurs only in men. The tablets must not be taken by women or by children).

Take special care with Finisol
Finisol can affect a blood test called PSA. If you have a PSA test done, tell your doctor that you are taking Finisol.

BPH is not cancer and does not lead to cancer, but the two conditions can be present at the same time. Before starting you on Finisol, it is likely that your doctor will perform some simple tests to check whether you have prostate cancer. Your doctor will evaluate your symptoms and their possible causes. Talk to your doctor if you have any questions.
Before starting treatment with Finiol, the treating physician should exclude that the difficulty of you to pass urine is due to tumour growth pattern of the prostate.

Caution should be taken if you have liver problems, since the active substance of finasteride is metabolised in the liver.

The medicine contains yellow. It may cause allergic reactions.

Taking other medicines
Finiol does not usually interfere with other medicines. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Finiol with food and drink
You can take Finiol with or without food.

Pregnancy and breast-feeding
If the active ingredient in Finiol is absorbed by a woman who is pregnant with a male baby, it may affect the normal development of the baby's sex organ. Therefore, women who are or may potentially be pregnant, should not be exposed to Finiol. They should not take Finiol. In addition, they should not handle broken or crushed tablets or be exposed to the drug through sexual contact with a man taking Finiol. Therefore, if your sexual partner is or may potentially be pregnant, you must avoid exposing her to your semen which could contain a tiny amount of the drug - for example, by using a condom during sexual activity. If a woman who is pregnant comes into contact with the active ingredient in Finiol, a doctor should be consulted. Whole Finiol tablets are coated to prevent contact with the active ingredient during normal handling.

Ask your doctor or pharmacist if you have any questions.

Driving and using machines
Finiol has no influence on the ability to drive and use machines.

3. HOW TO TAKE FINIOL

Always take Finiol exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one tablet containing 5 mg finasteride to be taken by mouth once a day with or without food.

Your doctor may prescribe Finiol along with another medicine called dutasteride to help you control your BPH.

If you take more Finiol than you should
If you take too many tablets by mistake, contact your doctor immediately.

If you forget to take Finiol
If you miss a dose, just carry on with the next one as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Finiol
In order to treat your symptoms and control your BPH effectively, it is important that you continue to take Finiol for as long as your doctor prescribes, even if you do not feel as
immediate benefit. Some patients show early improvement in symptoms, but you may need to take Finiol for at least six months to see if it improves your symptoms. Finiol works best when taken long term.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Finiol can cause side effects, although not everybody gets them.

Side effects due to Finiol may include:

*Common (affects 1 to 10 users in 100):*
changes with ejaculation (such as a decrease in the amount of semen released during sex which does not appear to interfere with normal sexual function), impotence (an inability to have an erection), less desire to have sex

*Uncommon (affects 1 to 10 users in 1,000):*
problems with ejaculation, breast swelling and/or tenderness, rash

*Rare (affects 1 to 10 users in 10,000):*
testicular pain, allergic reactions such as itching, rashes and swelling of the lips and face

*Very rare (affects less than 1 user in 10,000):*
breast secretion, breast lumps that are surgically removed

In some cases, such side effects disappeared while the patient continued to take Finiol. If symptoms persist, they usually resolved on discontinuing Finiol.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. It will help if you make a note of what you experienced, when it started and how long it lasted.

5. **HOW TO STORE FINIOL**

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Finiol after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Finiol contains
- The active substance is finasteride.
- The other ingredients are: microcrystalline cellulose, pregelatinised maize starch, sodium starch glycollate, iron oxide yellow (E172), sodium docusate, magnesium stearate.
- Coating: hypromellose, titanium dioxide (E171), tlc, propylene glycol, indigo carmine (E110), quinoline yellow FCF (E104), sunset yellow FCF (E110).

What Finiol looks like and contents of the pack

Finiol is available as blue, round, biconvex, film-coated tablets scored on one side.

Finiol is available in blister packs of 15 or 30 or 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

Marketing Authorization Holder
Pharmathen S.A.
6 Dervenakion str.
Pallini 15351
Athens
Greece

Manufacturer
Pharmathen S.A.
6 Dervenakion str.
Pallini 15351
Athens
Greece

This leaflet was last approved in 07/2009.
Module 4

Labelling
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTBOARD BOX

1. **NAME OF THE MEDICINAL PRODUCT**

Finiol 5mg film – coated tablets
Finasteride

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 5 mg of finasteride

3. **LIST OF EXCIPIENTS**

Contains sunset yellow FCF (E110)

4. **PHARMACEUTICAL FORM AND CONTENTS**

15 film – coated tablets
30 film – coated tablets
100 film – coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

This medicine is for use in men only.

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmathen S.A., 6 Dervenakion str. 153 51 - Pallini Attiki, Greece

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 17277/0018

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Finiol 5 mg
| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
| ALUMINIUM FOIL/ BLISTER |

1. **NAME OF THE MEDICINAL PRODUCT**

   Finiol 5mg film – coated tablets
   Finasteride

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Pharmathen S.A.

3. **EXPIRY DATE**

   EXP:

4. **BATCH NUMBER**

   Lot:

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTBOARD BOX

1. NAME OF THE MEDICINAL PRODUCT

Nikiid 5mg film – coated tablets
Finasteride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of finasteride

3. LIST OF EXCIPIENTS

Contains: sunse yellow FCF (E110)

4. PHARMACEUTICAL FORM AND CONTENTS

15 film – coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This medicine is for use in men only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmatherm S.A., 6 Dervenakion str. 133 51 - Fallini Attiki, Greece

### 12. MARKETING AUTHORISATION NUMBER(S)

PL 17277/0019

### 13. BATCH NUMBER

Lot:

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Niktid 5 mg

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**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**ALUMINIUM FOIL/BLISTER**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tr>
<td>Niktid 5 mg film – coated tablets</td>
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<th>5. OTHER</th>
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</table>
1. **NAME OF THE MEDICINAL PRODUCT**

Finasteride 5mg film-coated tablets

Finasteride

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 5mg of finasteride

3. **LIST OF EXCIPIENTS**

Contains: sunset yellow FCF (E110)

4. **PHARMACEUTICAL FORM AND CONTENTS**

15 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

This medicine is for use in men only.

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmathen S.A., 6 Dervenakion str. 153 51 - Pallini Attiki, Greece

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 17277/0020

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Finasteride 5 mg

### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**ALUMINIUM FOIL / BLISTER**

1. **NAME OF THE MEDICINAL PRODUCT**

Finasteride 5mg film-coated tablets

Finasteride

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Pharmathen S.A.

3. **EXPIRY DATE**

EXP:

4. **BATCH NUMBER**

Lot:

5. **OTHER**
Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Finasteride 5mg tablets, is approvable.

Several points for consideration with regard to the bioequivalence study and Pharmacovigilance system were raised during the first assessment step of the procedure. On Day 180 all points with regard to the bioequivalence study have been resolved. The Applicant’s Pharmacovigilance system was satisfactory on Day 205 of the procedure.

EXECUTIVE SUMMARY

Problem statement

These are DC applications for Finasteride 5 mg film coated tablets under article 10 (1) of Directive 2001/83/EC, as amended, with UK as RMS. The application is submitted under article 10(1) of Directive 2001/83/EC as amended, with Proscar 5 mg (PL 00025/0279), licensed to Mark Sharp & Dohme in 1992 as cross reference product. Finasteride 5mg tablets are used for the treatment and control of benign prostatic hyperplasia for regression of an enlarged prostate, improve urinary flow and improvement of other symptoms associated with BPH.

About the product

Finasteride is an azasteroid that inhibits the type-2 isoform of 5α-reductase, the enzyme responsible for conversion of testosterone to the more active dihydrotestosterone, and therefore has anti-androgenic properties. It is given by mouth in a dose of 5 mg daily in the management of benign prostatic hyperplasia to cause regression of the enlarged prostate and to improve symptoms; it may reduce the incidence of acute urinary retention and the need for surgery. Response may be delayed and treatment for 6 months or more may be required to assess whether benefit has been achieved.

The submitted dossier is adequate and sufficient.

Please note that the name of the product in RMS was changed at day-105. However, the naming is a national issue and should be considered during the national phase of the DCP.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

QP responsible for batch release of the finished product has provided a declaration for GMP compliance of the API manufacturer.
The finished product is manufacturer has provided a GMP certificate, issued by Greek health authority to support the manufacture of tablets and solid dosage forms.
The Applicant confirms that the bioequivalence study was conducted according to the GCP principles.
SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug Substance
Finasteride 5mg tablets are used for the treatment and control of benign prostatic hyperplasia for regression of an enlarged prostate, improve urinary flow and improvement of other symptoms associated with BPH

The drug substance Finasteride is described in the European Pharmacopoeia (Ph. Eur.).

The drug substance has practically insoluble in water, freely soluble in ethanol and in methylene chloride and exhibits polymorphisim. Form III is used which is well characterised by XRD. It is manufactured by two processes. The synthesis process has been satisfactorily described and is adequate.

The drug substance specification and analytical methods comply with Ph. Eur monograph. The impurity profiles and limits are in line with Ph. Eur monograph of finasteride. The container and closure system used has been adequately described. The stability data of the drug substance has been provided for storage under accelerated and long term storage condition and is satisfactory. Proposed re-test period is acceptable.

Drug Product
Finasteride-Pharmathen 5 mg film-coated tablets are presented as blue, round, biconvex, film-coated tablets scored on one side. The drug product is proposed to be marketed are packed into PVC 250µm / PE 25µm /PVDC 90g/m² / Aluminium 20µm blisters. All the excipients are well recognized for their role in pharmaceutical formulations and comply with their Ph. Eur monographs.

The drug product is manufactured by wet granulation using methanol as granulating solvent. Satisfactory details of the manufacturing process and in-process controls are provided.

The drug product specification is satisfactory. Satisfactory batch analysis data and stability data is provided only for production scale batches has been provided. Stability data has been provided for 36 months, and all the values remain within acceptance limits.

All the quality points are now resolved.

Non clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of finasteride are well known. As finasteride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

There are no objections to approval of Finasteride 5 mg film coated tablets from a non-clinical point of view.
Clinical aspects

To support the application, the applicant has submitted one bioequivalence study to determine the relative rate and extent of absorption from the two formulations of finasteride.

Study design
A single dose, randomised, two-sequence, two-period, crossover BE study under fasting conditions.

Test and reference products
Test Product (A): Finasteride, Pharmathen SA, Greece
Manufactured by: Famar SA, Greece

Reference Product (B): Proscar 5 mg Tablets (MSD, Greece, MAH in Greece Vianex SA)

Assayed product content was 105% for the test and 100.5% for the reference product.

Population(s) studied and clinical part of the study
28 male healthy Caucasian volunteers with age range from 19 to 39 years were entered in the study. Inclusion and exclusion criteria were presented and acceptable. All volunteers completed both study periods. According to the protocol, PK analysis and BE conclusion was based on the 24 first subjects who completed the study. One subject had non-detectable levels of finasteride plasma concentrations in both periods and was therefore excluded from the data analysis. This subject was replaced by the next available subject with the same randomisation sequence. Study drug was administered after an overnight fast with 180 ml water. 16 blood samples were collected at pre-dose (0.0) and at 30, 60, 75, 90, 105, 120 minutes and at 2.25, 2.5, 3, 3.5, 4, 6, 8, 10, 12 and 24 hours post-dose after administration of each product with washout period of 7 days between study drug administrations. One adverse event (fever) was reported during the study.

Analytical methods
Plasma concentrations of finasteride were determined with LC-MS/MS. Study samples were analysed in a total of 15 analytical sequences, within-study accuracy and precision was within the acceptance range based on back-calculated concentrations of quality control (QC) samples and calibration curve samples. Calibration curve samples at 7 levels ranged from 3 ng/ml to 200 ng/ml. Three sets of QC samples at three concentration levels (9 ng/ml, 100 ng/ml, 180 ng/ml) were included in each analytical sequence. Recovery after liquid extraction of plasma samples with diethyl ether/n-hexane 95% (80:20) was determined at three concentration levels for finasteride, and at one level for the internal standard (cyproterone acetate). Mean recovery was 99.6%(CV=18.2% at 9ng/ml) to 69.8% (CV=9.5% at 160 ng/ml) for finasteride, 73%-87% (CV=6%-28%) for internal standard. Analyte stability at two concentration levels at various storage conditions was shown. Long term stability in plasma was shown for 33 days at -20°C, this period did not cover the real storage time. Peak area ratios of finasteride to the internal standard were used from chromatograms and plotted against respective standard concentrations. Linear regression analysis was performed using a 1/x weighting factor. Concentrations below lower limit of quantification were treated as zero in PK analysis.

Pharmacokinetic Variables and Statistical methods
Individual plasma concentrations were tabulated.
Pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, T1/2 were determined. AUC0-t was calculated using the linear trapezoidal method. PK parameters were calculated using the EquivTest 1.0. PK parameters for each individual were tabulated and graphically presented. Using the EquivTest 1.0 the analysis of variance with sequence, subject within sequence, period and product effects was applied to the ln-transformed AUCt, AUCinf, Cmax. The classical shortest 90%CI was computed.
Results
Pharmacokinetic parameters of the Test and Reference product are presented below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test</th>
<th>Reference</th>
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<tbody>
<tr>
<td>AUC_{0-1} (ng*min/mL)</td>
<td>14119.65 ± 5689.376</td>
<td>13720.15 ± 5250.285</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng*min/mL)</td>
<td>17439.4 ± 6466.663</td>
<td>17288.32 ± 6063.454</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>35.54 ± 10.861</td>
<td>34.82 ± 10.932</td>
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**Assessor’s comment**

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, a bioequivalence study should be submitted for the immediate release product to support a generic application. Bioequivalence study submitted by the applicant was performed according to the respective NfG and GCP requirements. The 90% confidence intervals for the ratio of the AUC and $C_{max}$ lie within the acceptance criteria of 80-125%.

**Pharmacovigilance system**

Satisfactory

**BENEFIT RISK ASSESSMENT**

The benefit-risk ratio is considered favourable. No post-marketing data is available. The medicinal product has not been marketed in any country. The safety profile of finasteride containing products is well established and the data show that benefits of finasteride outweigh potential risks.
Module 6

Steps taken after procedure

No non-confidential changes have been made to the Marketing Authorisations.