

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

Profal, film coated tablets, 1 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 1 mg of finasteride.

Excipient of known effect: Lactose monohydrate

For the full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Reddish brown, round, biconvex, film coated tablets marked 'F1' on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Profal is indicated for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

Profal is not indicated for use in women (see **4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation**) or children.

Profal is not effective in postmenopausal women with androgenetic alopecia.

### 4.2 Dose and method of administration

*Adults:*

The recommended dosage is one 1 mg tablet daily. Profal may be taken with or without food. In general, daily use for 3 months or more is necessary before increased hair growth and/or prevention of further hair loss is observed. Continued use is recommended to obtain maximum benefit. Withdrawal from the treatment leads to reversibility of effect within 12 months.

### Special Populations:

*Children:*

Profal is not indicated for use in children.

*Elderly:*

Clinical studies with Finasteride tablets have not been conducted in elderly men with male pattern hair loss.

*Renal impairment:*

No adjustment in dosage is necessary in non-dialysed patients with renal impairment.

### 4.3 Contraindications

Profal is not indicated for use in women or children.

Profal is contraindicated in the following:

-Use in women when they are or may potentially be pregnant (see **4.1 Therapeutic indications, 4.4 Special warnings and precautions for use and 4.6 Fertility, pregnancy and lactation**).

-Hypersensitivity to any component of this product.

#### **4.4 Special warnings and precautions for use**

In clinical studies with Finasteride in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng /mL at Month 12. When finasteride is used for treatment of male pattern hair loss in older men who also have benign prostatic hyperplasia (BPH), consideration should be given to the fact that, in older men with BPH, PSA levels are decreased by approximately 50%.

Breast cancer has been reported in men taking finasteride 1 mg during 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.

##### *Pregnancy*

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 male fetuses. 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. (see **4.3 Contraindications** and **4.6, Fertility, pregnancy and lactation**)

##### *Paediatric Use*

Profal is not indicated for use in children.

##### *Use in the Elderly*

Clinical studies with Finasteride tablets have not been conducted in elderly men with male pattern hair loss.

#### **4.5 Interaction with other medicines and other forms of interaction**

No medicine interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked medicine metabolising enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, glyburide, propranolol, theophylline, and warfarin and no interactions were found.

Although specific interaction studies were not performed, in clinical studies finasteride doses of 1 mg or more were used concomitantly with ACE inhibitors, acetaminophen, alpha blockers, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

#### **4.6 Fertility, pregnancy and lactation**

##### **Fertility:**

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,000 times the recommended human dose of 1 mg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen.

In sexually mature rats treated with the same dose of finasteride, there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility and fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment.

The decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man who do not form copulatory plugs. No medicine-related effect on testes or on mating performance has been seen in rats or rabbits.

**Pregnancy:**

Finasteride is contraindicated for use in women when they are or may potentially be pregnant. (see **4.1 Therapeutic indications**, **4.4 Special warnings and precautions for use** and **4.6 Fertility, pregnancy and lactation**).

Because of the ability of Type II 5 $\alpha$ -reductase inhibitors to inhibit conversion of testosterone to DHT in some tissues, these medicines, including finasteride, may cause abnormalities of the external genitalia of a male foetuses when administered to a pregnant woman.

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 male foetuses. 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.

Dose-dependant development of hypospadias was observed in the male offspring of pregnant rats given finasteride at doses ranging from 100  $\mu$ g/kg/day to 100 mg/kg/day (5 to 5,000 times the recommended human dose of 1 mg/day) at an incidence of 3.6 to 100%. Additionally, pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at doses  $\geq$ 30  $\mu$ g/kg/day ( $\geq$ 1.5 times the recommended human dose of 1 mg/day), and decreased anogenital distance when given finasteride in doses 3  $\mu$ g/kg/day (approximately one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced has been defined in male rats as Days 16-17 of gestation.

The changes described above are expected pharmacological effects of Type II 5 $\alpha$ -reductase inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed *in utero* to finasteride are similar to those reported in male infants with a genetic deficiency of Type II 5 $\alpha$ -reductase. No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Administration of finasteride to rats during the late gestation and lactation period resulted in slightly decreased fertility in first generation male offspring (3 mg/kg/day; 150 times the recommended human dose of 1 mg/day). No developmental abnormalities have been observed in first generation male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 4,000 times the recommended human dose of 1 mg/day) with untreated females.

No evidence of malformations has been observed in rabbit foetuses exposed to finasteride in utero from Days 6-18 of gestation at doses up to 100 mg/kg/day (5,000 times the recommended human dose of 1 mg/day).

The *in utero* effects of finasteride exposure during the period of embryonic and foetal development were evaluated in the rhesus monkey (Gestation Days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male foetuses. In confirmation of the relevance of the rhesus model for human foetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) 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.

**Breast Feeding:**

Profal 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**

There are no data to suggest that finasteride tablets affect the ability to drive or use machinery.

#### **4.8 Undesirable effects**

Finasteride is generally well tolerated. Adverse effects, which usually have been mild, generally have not required discontinuation of therapy.

##### *Adverse events identified during clinical trials*

Finasteride for male pattern hair loss has been evaluated for safety in clinical studies involving more than 3,200 men. In three 12-month, placebo-controlled, double-blind, multicenter studies of comparable design, the overall safety profiles of finasteride and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 1.7% of 945 men treated with finasteride and 2.1% of 934 men treated with placebo.

In these studies, the following medicine-related adverse experiences were reported in  $\geq 1\%$  of men treated with finasteride:

- decreased libido (finasteride, 1.8% vs. placebo, 1.3%)
- erectile dysfunction (1.3%, 0.7%).
- decreased volume of ejaculate (0.8%, 0.4%)

Resolution of these adverse effects occurred in men who discontinued therapy with finasteride and in many who continued therapy. In a separate study, the effect of finasteride on ejaculate volume was measured and was not different from that seen with placebo. The incidence of each of the above adverse effects decreased to  $\leq 0.3\%$  by the fifth year of treatment with finasteride.

##### *Breast Cancer*

During the 4-to-6-year placebo and comparator-controlled Medical Therapy of Prostatic Symptoms (MTOPS) study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride 5 mg, but no cases in men not treated with finasteride 5 mg. During the 4-year, placebo controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo treated men, but no cases in men treated with finasteride 5 mg. During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT) that enrolled 18,882 men, there was 1 case of breast cancer in men treated with placebo. There have been post-marketing reports of male breast cancer with the use of finasteride 1 mg and 5 mg. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown (see **4.4 Special warnings and precautions for use**).

##### *Prostate Cancer*

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 5 mg and 1147 (24.4%) men receiving placebo. In the finasteride 5 mg group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in placebo group. 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 5 mg and tumours with Gleason scores of 7-10 is unknown. The significance of these results for ReGen are unknown as the use of finasteride 1mg was not studied.

##### *Adverse events identified during post-marketing experience*

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.

##### *Immune system disorders*

- hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face.

#### *Psychiatric disorders*

- depression

#### *Reproductive system and breast disorders*

- ejaculation disorder
- breast tenderness and enlargement;
- testicular pain;
- erectile dysfunction that continued after discontinuation of treatment;
- male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

#### *Cardiac disorders*

- palpitation

#### *Hepatobiliary disorders*

- increased hepatic enzymes

### **Reporting of suspected adverse reactions:**

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

### **4.9 Overdose**

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse effects.

No specific treatment for over dosage with finasteride tablets is recommended.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Urologicals (Testosterone-5-alpha reductase inhibitors), ATC code: G04CB01

Finasteride is a competitive and specific inhibitor of Type II 5 $\alpha$ -reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ( $t_{1/2}$  ~30 days). Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT), resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching significant suppression within 24 hours of dosing.

Hair follicles contain Type II 5 $\alpha$ -reductase. In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT. Administration of finasteride decreases scalp and serum DHT concentrations in these men. In addition, men with a genetic deficiency of Type II 5 $\alpha$ -reductase do not suffer from male pattern hair loss. These data and the results of the clinical studies confirm that finasteride inhibits the process responsible for miniaturisation of the scalp hair follicles, leading to reversal of the balding process.

## 5.2 Pharmacokinetic properties

### *Absorption*

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 80%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately two hours after dosing and the absorption is complete after 6-8 hours.

### *Distribution*

Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 litres.

There is modest accumulation of finasteride in plasma after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL and was reached 1 to 2 hours post-dose; AUC<sub>(0-24 hr)</sub> was 53 ng.hr/mL.

Finasteride has been recovered in the cerebrospinal fluid (CSF) but the medicine does not appear to concentrate preferentially to the CSF. A very small amount of finasteride has also been detected in the seminal fluid of subjects receiving finasteride.

### *Metabolism*

Finasteride is metabolised primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of <sup>14</sup>C-finasteride in man, two metabolites of finasteride were identified that possess only a small fraction of the 5 $\alpha$ -reductase inhibitory activity of finasteride.

### *Elimination*

Following an oral dose of <sup>14</sup>C-finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged medicine was excreted in the urine) and 57% of total dose was excreted in the faeces.

Plasma clearance is approximately 165 mL/min.

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

### *Characteristics in specific group of patients*

No adjustment in dosage is necessary in non-dialysed patients with renal impairment.

## 5.3 Preclinical safety data

### *Carcinogenicity*

No evidence of a tumorigenic effect was observed in a 24-month study in rats receiving doses of finasteride up to 320 mg/kg/day (16,000 times the recommended human dose of 1 mg/day).

In a 19-month carcinogenicity study in mice, a statistically significant ( $p \leq 0.05$ ) increase in the incidence of testicular Leydig cell adenoma was observed at a dose of 250 mg/kg/day (12,500 times the recommended human dose of 1 mg/day); no adenomas were seen in mice given 2.5 or 25 mg/kg/day (125 and 1,250 times the recommended human dose of 1 mg/day, respectively).

In mice at a dose of 25 mg/kg/day and in rats at a dose of  $\geq 40$  mg/kg/day (1,250 and  $\geq 2,000$  times the recommended human dose of 1 mg/day, respectively), an increase in the incidence of Leydig cell hyperplasia was observed.

A positive correlation between the proliferative changes of the Leydig cells and the increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high

doses of finasteride. This suggests the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

No medicine-related Leydig cell changes were seen in either rats or dogs treated with finasteride for one year at doses of 20 mg/kg/day and 45 mg/kg/day (1,000 and 2,250 times the recommended human dose of 1 mg/day, respectively) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (125 times the recommended human dose of 1 mg/day).

#### *Mutagenesis*

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 an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 µmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 µmol) used in the *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increases in chromosome aberration were observed with finasteride at the maximum tolerated dose (250 mg/kg/day; 12,500 times the recommended human dose of 1 mg/day).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate  
Microcrystalline cellulose (E460)  
Pregelatinised maize starch  
Lauroyl macrogolglycerides  
Sodium starch glycolate (Type A)  
Magnesium stearate (E572)  
Opadry 03F34739 Pink (as colouring agent)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

Alu-Alu blister strips.

Packs of 28 tablets.

### **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7. MEDICINE SCHEDULE**

Prescription Only Medicine

## **8. SPONSOR**

Teva Pharma (New Zealand) Limited  
PO Box 128 244  
Remuera

Auckland 1541  
Telephone: 0800 800 097

## **9. DATE OF FIRST APPROVAL**

28<sup>th</sup> October 2010

## **10. DATE OF REVISION OF THE TEXT**

23<sup>rd</sup> August 2017

## **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
Complete data sheet	Update to the SPC-style format