New Zealand Data Sheet

1. PRODUCT NAME

PROCUR® 50 mg and 100 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PROCUR 50 mg tablet contains 50 mg of cyproterone acetate.
Each PROCUR 100 mg tablet contain 100 mg of cyproterone acetate.

Excipient(s) with known effect

PROCUR tablet contains lactose monohydrate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PROCUR 50 mg Tablets are white to off-white, round, flat, tablets having a score and embossed 50 on one side and plain on the other.

PROCUR 100 mg Tablets are white to off white, capsule shaped tablets having a score on one face and embossed 100 on the other.

PROCUR (Cyproterone acetate) is an antiandrogenic hormone preparation. Cyproterone acetate is a white or almost white crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in acetone, soluble in methanol, sparingly soluble in ethanol.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Men

- Antiandrogen treatment in inoperable carcinoma of the prostate
- Reduction of drive in sexual deviations

Women

- Severe signs of androgenization, e.g. very severe hirsutism in the female, severe androgenetic alopecia, often attended by severe forms of acne and/or seborrhoea.

4.2. Dose and method of administration

Dose

Adult Men

Antiandrogen treatment in inoperable carcinoma of the prostate

To eliminate the effect of adrenocortical androgens after orchiectomy: two 50 mg tablets once or twice daily (= 100-200 mg total daily dose). Without orchiectomy: two 50 mg tablets twice to three times daily (= 200-300 mg total daily dose).

Treatment should not be interrupted, nor the dosage reduced after improvement or remissions have occurred.

To reduce the initial increase of male sex hormones in treatment with LH-RH agonists: Initially two 50 mg tablets PROCUR twice daily (= 200 mg total daily dose) alone for 5 - 7 days followed by two 50 mg tablets PROCUR twice daily (= 200 mg total daily dose) for 3 - 4 weeks together with an LH-RH agonist in the dosage recommended by the manufacturer.

To eliminate the effect of adrenocortical androgens in treatment with LH-RH agonists: Continuation of the antiandrogen therapy with two 50 mg tablets PROCUR once to twice daily (= 100-200 mg total daily dose).

Reduction of drive in pathologically altered or increased sexuality

The tablets are to be taken with some liquid after meals. The individual dose will be determined by the response. Generally, the treatment is started with one 50 mg tablet twice daily. It may be necessary to increase the dose to two 50 mg tablets twice daily or even two 50 mg tablets three times daily for a short period of time. When a satisfactory result is achieved, an attempt should be made to maintain the therapeutic effect with the lowest possible dose. Quite often 1/2 a 50 mg tablet twice daily is sufficient.

When establishing the maintenance dose or when discontinuing the preparation, one should not reduce the dosage abruptly, but gradually. To this end, the daily dose should be reduced by one 50 mg tablet or, better, half a 50 mg tablet, at intervals of several weeks.

To stabilise the therapeutic effect, it is necessary to take PROCUR over a protracted period of time, if possible, with the simultaneous use of psychotherapeutic measures.

Adult women

Pregnant women must not take cyproterone acetate. Therefore, pregnancy must be excluded before the start of therapy.

In women of childbearing age, the treatment is commenced on the 1st day of the cycle (= first day of bleeding). Only women with amenorrhoea or menstrual bleeding at very irregular intervals can

start the treatment immediately. In this case, the first day of treatment is to be regarded as the 1st day of the cycle and the following recommendations then observed as normal.

For hirsutism secondary to female androgenisation; the usual starting dose should be 1 tablet of cyproterone acetate 50 mg taken daily for 10 days per month (from the 1st to the 10th day of the cycle). Once a satisfactory response has been attained it is usually possible to reduce the dose further. Doses as low as 10 mg a day for 10 days per month have been shown to be adequate for maintenance therapy in this condition.

For other severe signs of androgenisation; 2 tablets of cyproterone acetate 50 mg are to be taken daily with some liquid after a meal from the 1st to the 10th day of the cycle (=for 10 days). In addition, these women receive a progestogen-oestrogen preparation, to provide the necessary contraceptive protection and to stabilise the cycle. An appropriate combined oral contraceptive preparation should be commenced on day 1 of the cycle as directed.

Women receiving the cyclical combined therapy should keep to a particular time of the day for tablet taking. If more than 12 hours elapse from this time, contraceptive protection in this cycle may be reduced. **Attention is drawn to the special notes (especially on contraceptive reliability and to the missed tablet recommendations) in the product information for the combined oral contraceptive preparation being taken in conjunction with PROCUR.** If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed.

Missed cyproterone acetate tablets may diminish the therapeutic efficacy and may lead to intermenstrual bleeding. The missed PROCUR tablet should be disregarded (no double dose should be taken to make up for the missed tablet) and tablet taking resumed at the regular time together with the combined oral contraceptive preparation.

A 7-day tablet-free interval is observed after 21 days during which time a withdrawal bleeding occurs. Exactly 4 weeks after the first course was started i.e., on the same day of the week, the next cyclical course of combined treatment is started, regardless of whether bleeding has stopped or not. If no bleeding occurs during the tablet free or 7-day placebo tablet interval, the treatment must be interrupted, and pregnancy must be excluded before tablet taking is resumed.

Following clinical improvement, the daily dose of PROCUR 50 mg may be reduced to 1 or ½ tablet during the 10 days on which it is given in each treatment cycle. The dose regimen for the combined oral contraceptive preparation remains unchanged. Re-evaluate the treatment with PROCUR 50 mg at the start of the menopause. Long-term use (years) of PROCUR 50 mg should be avoided (see section 4.4 Special warnings and precautions - Meningioma)

In postmenopausal or hysterectomised patients, PROCUR may be administered alone. According to the severity of the complaints, the average dose should be ½ to 1 tablet PROCUR 50 mg once daily for 21 days, followed by a 7-day tablet-free interval.

The length of treatment depends on the severity of the pathological signs of androgenisation and response to treatment. Treatment is usually carried out over several months initially. Acne and

seborrhoea usually respond sooner than hirsutism or alopecia. Hirsutism and alopecia are likely to recur when the treatment is stopped.

Paediatric population

PROCUR is not recommended for use in female patients before conclusion of puberty. There are no data suggesting the need for dosage adjustment in female patients who have completed puberty.

PROCUR is not recommended for use in male children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

PROCUR must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.

Special populations

Elderly population

There are no data suggesting the need for dosage adjustment in elderly patients.

Renal impairment

There are no data suggesting the need for dosage adjustment in patients with renal impairment.

Hepatic impairment

The use of cyproterone acetate is contraindicated in patients with liver diseases

Method of Administration

The tablets are to be taken with some liquid after meals.

4.3. Contraindications

- Hypersensitivity to any of the ingredients of PROCUR
- Pregnancy
- A history of jaundice or persistent itching during a previous pregnancy
- A history of herpes in pregnancy
- Lactation
- Liver diseases
- Previous or existing liver tumours (in carcinoma of the prostate only if these are not due to metastases)
- Meningioma or a history of meningioma
- Wasting diseases (with the exception of carcinoma of the prostate)
- Dubin-Johnson syndrome
- Rotor syndrome
- Severe chronic depression
- Previous or existing thromboembolic processes

- Severe diabetes with vascular changes
- Sickle-cell anaemia.

With regards to the cyclical combination therapy of severe signs of androgenization, attention is also drawn to the data on contraindications contained in the product information for progestogen-oestrogen containing preparation is used in addition to PROCUR.

4.4. Special warnings and precautions for use

General

During treatment liver function, adrenocortical function and red blood cell count should be checked regularly.

Liver

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure has been observed in patients treated with cyproterone acetate. At dosages of 100-300 mg, cases with fatal outcome have been reported. Most reported fatal cases were in men with advanced carcinoma of the prostate although cases involving women and patients treated with lower doses have been reported.

Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should be withdrawn, unless hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

Cases of benign and malignant liver tumours, which may lead to life-threatening intraabdominal haemorrhage, have been observed after the use of cyproterone acetate. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnostic considerations.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above. If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment with cyproterone acetate must be stopped (see section 4.3).

Diabetes

Strict medical supervision is necessary if the patient suffers from diabetes, because the requirement for oral antidiabetics or insulin can change during cyproterone acetate treatment (see section 4.3).

Shortness of breath

A sensation of shortness of breath may occur under high-dosed treatment with cyproterone acetate. The differential diagnosis in such cases must include the stimulating effect on breathing known for progesterone and synthetic progestogens which is accompanied by hypocapnia and compensated respiratory alkalosis and which is not considered to require treatment.

Thromboembolic events

The occurrence of thromboembolic events has been reported in patients using cyproterone acetate although a causal relationship has not been established. Patients with previous arterial or venous thrombotic / thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or with a history of cerebrovascular accidents or with advanced malignancies are at increased risk of further thromboembolic events.

Adrenocortical function

During treatment adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of cyproterone acetate with high doses.

Anaemia

Anaemia has been reported during treatment with cyproterone acetate. Therefore, the red- blood cell count should be checked regularly during treatment.

Lactose

PROCUR tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal-absorption should not take this medicine.

Special populations

Specifically to be observed in women

Before the start of therapy, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out. Serious organic causes of androgenisation, e.g. Cushing's syndrome, ovarian tumours, adrenal carcinoma and adrenogenital syndrome should be excluded. Pregnancy must be excluded at the time of commencing treatment in women of child-bearing potential. If, during the combined treatment, spotting occurs during the 3 weeks in which the tablets are being taken, tablet-taking should not be interrupted. However, if persistent or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic diseases.

With regard to the additional use of a combined oral contraceptive preparation, attention is drawn to all the data contained in the product information for this product.

Specifically to be observed in men

Spermatogenesis: In men of procreative age, for whom fertility could be important after conclusion of the medication, it is advisable to make at least one control spermatogram as a precaution before the start of treatment in order to counter any unjustified claims of later infertility as a result of the antiandrogen therapy. Spermatogenesis has taken 3-20 months to return to normal after discontinuing therapy.

The sexual drive-reducing effect of PROCUR can be diminished under the influence of alcohol.

In patients with inoperable carcinoma of the prostate presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia or from severe diabetes with vascular changes, a careful risk: benefit evaluation must be carried out in each individual case before cyproterone acetate is prescribed.

As with other antiandrogenic treatments, in male patients long-term androgen deprivation with Cyproterone acetate may lead to osteoporosis.

4.5. Interaction with other medicines and other forms of interaction

Diabetes: The requirement for oral antidiabetics or insulin can change with cyproterone acetate treatment.

Chronic alcoholism: The sexual drive-reducing effect of cyproterone acetate can be diminished under the influence of alcohol.

Other interactions: although clinical interaction studies have not been performed, since this drug is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 inhibit the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as e.g. rifampicin, phenytoin and products containing St. John´s wort may reduce the levels of cyproterone acetate.

Statins: The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMGCoA inhibitors (statins), which are primarily metabolised by CYP3A4, are co-administered with high therapeutic cyproterone acetate doses since they share the same metabolic pathway.

Based on *in vitro* CYP450 studies, the recommended clinical doses are likely to inhibit CYP2C8, and an inhibition of the CYP 2C9, 2C19, 3A4, and 2D6 is also possible at high therapeutic cyproterone acetate doses of 3 times 100 mg per day.

4.6. Fertility, pregnancy and lactation

Pregnancy

The administration of PROCUR during pregnancy is contraindicated, see section 4.3.

Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approx. day 45 of pregnancy) could lead to signs of feminisation in male foetuses.

Breast-feeding

The administration of PROCUR during lactation is contraindicated (see section 4.3) as small amounts of cyproterone acetate are excreted in human milk.

Fertility

The long-term effects on female fertility are not known with certainty. Refer to section 5.3 and 5.1.

4.7. Effects on ability to drive and use machines

It should be pointed out to patients whose occupation demands great concentration (e.g. road users, machine operators) that PROCUR can lead to tiredness and diminished vitality and can impair the ability to concentrate.

4.8. Undesirable effects

The most serious ADRs in patients receiving cyproterone acetate are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage, and thromboembolic events. The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above.

Men

The most frequently observed ADRs in male patients receiving cyproterone acetate are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

Over the course of several weeks cyproterone gradually impairs spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within several months of discontinuing therapy.

In male patients cyproterone occasionally leads to gynaecomastia (sometimes combined with tenderness to touch of the breast) which usually regresses after withdrawal of the preparation or reduction of the dose.

As with other antiandrogenic treatments, in male patients long-term androgen deprivation with cyproterone may lead to osteoporosis.

Women

The most commonly reported adverse drug reactions (ADRs) in female patients receiving cyproterone acetate are spotting, weight increase and depressed mood.

In women ovulation is inhibited under the combined treatment so that a state of infertility exists.

A feeling of tension in the breasts may occur. In individual cases, disturbances of liver function, some of them severe, have been reported with high-dosed cyproterone treatment.

Changes in body weight are possible.

Other adverse events reported at a low incidence were dysmenorrhoea, vaginal discharge, skin discolouration, striae.

Adverse reactions reported in clinical trials

The following adverse reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below:

Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) none known frequency (cannot be estimated from the available data).

General disorders and administration site conditions

Very common: tiredness

Investigations

Very common: weight increase

Nervous system disorders

Common: headache

Psychiatric disorders

Very common: diminished libido
Common: depressive moods

Vascular disorders

Common: thrombotic phenomena, see section 4.4.

Reproductive system and breast disorders

Common: mastodynia, irregular menstrual cycles

Skin and subcutaneous tissue disorders

Rare: rash

Gastrointestinal disorders

Common: nausea and other gastrointestinal complaints

Post-marketing information

The following adverse effects have been reported in users of cyproterone acetate and are based on post-marketing data and cumulative experience with cyproterone acetate. The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.

Men

Psychiatric disorders

Very common: libido decreased; Erectile dysfunction

Musculoskeletal and connective tissue disorders

Very rare: osteoporosis

Reproductive system and breast disorders

Very common: reversible inhibition of spermatogenesis
Common: gynaecomastia
;

Women

Psychiatric disorders

Uncommon: libido decreased
Rare: libido increased

Reproductive system and breast disorders

Very common: ovulation inhibited
Common: breast tenderness
Very rare: irregular menstrual periods

Unspecified

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Very rare: benign and malignant liver tumours*
None known frequency: meningioma*

Blood and the lymphatic system disorders

None known frequency: anaemia*

Immune system disorders

Rare: hypersensitivity reactions may occur.

Metabolism and nutrition disorders

Common: weight increased, or weight decreased.

Skin and subcutaneous tissue disorders

Uncommon: rash.

Psychiatric disorders

Common: depressed mood; Restlessness (temporary)

Hepato-biliary disorders

Common: hepatic toxicity including jaundice, hepatitis, hepatic failure*
Rare: increased liver enzymes
Very rare: liver function disturbance

Gastrointestinal disorders

Very rare: nausea GI complaints
None known frequency: intra-abdominal haemorrhage*

Cardiovascular disorders

Very rare: thrombotic phenomena; tachycardia

Reproductive system and breast disorders

Very rare: breast pain; galactorrhoea

Vascular disorders

None known frequency: thromboembolic events*†

General disorders and administration site conditions

Common: fatigue; hot flushes; sweating
Very rare: tiredness; sleep disturbances; headache

Respiratory, thoracic and mediastinal disorders

Common: shortness of breath*.

*For further information see section 4.4 Special warnings and precautions for use
† A causal relationship with cyproterone acetate has not been established

Reporting of suspected adverse reactions

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

4.9. Overdose

There is no clinical experience in overdose. Assessment and symptomatic treatment should be initiated as required.

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: sex hormones and modulators of the genital system, antiandrogens
ATC code: G03HA01.

Mechanism of action

Cyproterone acetate is an antiandrogenic hormone preparation.

Cyproterone acetate inhibits competitively the effect of androgens at androgen-dependent target organs e.g., it shields the prostate from the effect of androgens originating from the gonads and/or the adrenal cortex. Prostatic carcinoma and its metastases are in general androgen-dependent, cyproterone acetate therefore exerts a direct antiandrogenic action on the tumour and its metastases.

Cyproterone acetate in addition has a progestogenic action exerting a negative feedback effect centrally on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and hence to diminished production of testicular androgens. Treatment with cyproterone acetate in men results in a reduction of sexual drive and potency and inhibition of gonadal function. These changes are reversible following discontinuation of the therapy.

The antigonadotropic effect of cyproterone acetate is also exerted when the substance is combined with LHRH agonists. The initial increase of testosterone provoked by this substance group is decreased by cyproterone acetate.

In women, hirsutism is diminished, but also androgen-dependent loss of scalp hair and elevated sebaceous gland function are reduced. During the treatment ovarian function is inhibited.

Prolactin levels can increase slightly under higher doses of cyproterone acetate. Studies showed increased prolactin levels up to 20 ng/mL (normal range 5-15 ng/mL). There are no data for periods longer than 6 months.

5.2. Pharmacokinetic properties

Absorption

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range.

The ingestion of 50 mg of cyproterone acetate gives maximum serum levels of about 140 ng/ml at about 3 hours. Thereafter drug serum levels decline during a time interval of typically 24 to 120 hours, with a terminal half-life of 43.9 ± 12.8 h. The total clearance of cyproterone acetate from serum was determined to be 3.5 ± 1.5 ml/min/kg. The absolute bioavailability of cyproterone acetate is unknown. Relative bioavailability was calculated, in a study of eight young women, from a dose-corrected comparison of area under the curves of serum levels after 100 mg oral and 300 mg intramuscular depot administration and was found to be 80±30% when averaged over all volunteers (range 23%-119%).

Distribution

The major part of circulating cyproterone acetate is bound to serum albumin. In a study in 15 women receiving 2mg cyproterone acetate in combination with 35 µg ethinyloestradiol, the free fraction of cyproterone acetate was about 3.5-4%. Because protein binding is non- specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

Metabolism

Cyproterone acetate is metabolised by various pathways, including hydroxylation and conjugation. The main metabolite in human plasma is 15β-hydroxy derivative. Some dose parts are excreted unchanged with bile fluid. Phase 1 metabolism of cyproterone acetate is mainly catalysed by the cytochrome P450 enzyme CYP3A4.

Elimination

In a study in 6 women administered a ^{14}C labelled dose of 2mg cyproterone acetate in combination with 50 µg oestrogen, approximately 30% of the label was found in the urine and 58% in the faeces. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).

Steady state conditions

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, an accumulation of cyproterone acetate by a factor of about 3 can be expected in the serum during repeated daily administration.

5.3. Preclinical safety data

Genotoxicity

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that cyproterone acetate was capable of producing hepatocyte DNA adducts in rats, dogs and monkeys (and an increase in DNA-repair activity in rats) *in vivo* and also in freshly isolated rat and human liver cells in vitro. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutation. The clinical relevance of these findings presently remains uncertain.

Carcinogenicity

Long-term animal carcinogenicity studies were performed in rats and mice. In one rat study, an increased incidence of hepatomas was reported at oral dose levels of 50 mg/kg cyproterone acetate and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the liver pathology), the carcinogenic potential of cyproterone acetate in animals could not be determined.

Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans. However, it must be borne in mind that steroidal sex hormones can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

PROCUR tablets contains croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

PROCUR 50 mg tablet: blister pack, PVC/PVDC/Al, 20 and 50 tablets
PROCUR 50 mg tablet: HDPE bottle with PP screw cap, 20 and 50 tablets
PROCUR 100 mg tablet: blister pack, PVC/PVDC/Al, 50 tablets

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

14 December 2006

10. DATE OF REVISION OF THE TEXT

09 June 2020

Summary table of changes

Section Changed	Summary of new information
4.2	Updated information as per recommendations from MARC to clarify dosage instruction.
4.4	Updated information as per recommendations from MARC on hepatic toxicity, and additional information added to align with innovator product.
4.8	Updated information as per recommendations from MARC to clarify common hepatic reactions and presenting information according to reactions during treatment of men and reactions during treatment of women, and additional information added to align with innovator product.
4.5, 4.6, 5.1, 5.2	Addition of safety information to align with innovator product.
4.9 and 5.3	Updated safety information to align with innovator product.