APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TERONRED 250 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg abiraterone acetate. Contains sugar (lactose monohydrate).

Excipients with known effect

Each film-coated tablet contains 198,65 mg of lactose monohydrate and 6,38 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off white, oval shaped, film coated tablets, debossed with Dr. Reddy's logo on one side and "358" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERONRED 250 is indicated with low-dose corticosteroids (prednisone or

prednisolone) in adult males for the treatment of:

- high-risk metastatic hormone treatment naïve prostate cancer (mHNPC) or newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (LHRH agonist or surgical castration).

  High-risk is defined as having at least 2 of the following 3 risk factors:

  (1) Gleason score of ≥ 8,

  (2) presence of 3 or more bone lesions,

  (3) presence of measurable visceral (excluding lymph node disease) metastasis.
- metastatic castration resistant prostate cancer with bone metastases who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- metastatic advanced prostate cancer (castration resistant prostate cancer) who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

Posology

The recommended dose of TERONRED 250 is 1 000 mg (four 250 mg tablets) as a single daily dose that **must not be taken with food**. Taking TERONRED 250 with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Patients should be maintained on TERONRED 250 until radiographic progression and symptomatic/clinical progression and until PSA progression (confirmed 25 % increase over the patient's baseline/nadir).

Dosage of prednisone or prednisolone

For metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate

cancer (mHSPC), TERONRED 250 is used with 5 mg prednisone or prednisolone once daily.

For metastatic castration-resistant prostate cancer (mCRPC), TERONRED 250 is used with 10 mg prednisone or prednisolone daily.

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with TERONRED 250, every two weeks for the first three months of treatment and monthly thereafter.

Blood pressure, serum potassium and fluid retention should be monitored monthly (see section 4.4).

In the event of a patient missing the daily dose of TERONRED 250, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatic impairment

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted.

TERONRED 250 should not be used in patients with moderate or severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment with TERONRED 250 (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN] or bilirubin increases above 3 times the upper limit of normal), treatment should be withheld immediately until liver function tests are back to pre-treatment status (see section 4.4). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two

tablets) once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. Reduced doses should not be taken with food (see previous). If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, TERONRED 250 treatment should be discontinued and patients should not be re-treated with TERONRED 250.

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Paediatric population

There is no relevant use of TERONRED 250 in the paediatric population, as prostate cancer is not present in the paediatric population.

Method of administration:

TERONRED 250 is for oral use.

TERONRED 250 must be taken on an empty stomach, at least one hour before or at least two hours after eating a meal.

TERONRED 250 tablets should be swallowed whole with water.

Precautions to be taken before handling or administering TERONRED 250

Based on its mechanism of action, TERONRED 250 may cause harm to a developing foetus; therefore women (including healthcare professionals), who are pregnant or who may be pregnant should not handle TERONRED 250 without protection e.g. gloves (see sections 4.6 and 6.6).

4.3 Contraindications

TERONRED 250 is contraindicated in:

- Patients who have a known hypersensitivity to abiraterone acetate or its excipients listed in section 6.1.

- Women should not use TERONRED 250.
- Women who are pregnant, trying to get pregnant or may potentially be pregnant and women who are breastfeeding (see section 4.6).
- Moderate to severe hepatic impairment (Child-Pugh Class B and C) (see sections 4.2, 4.4 and 5.2).
- Concomitant administration with rifampicin (see section 4.5).
- TERONRED 250 with prednisone or prednisolone is contraindicated in combination with Ra-223 (radium 223).

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess

TERONRED 250 may cause hypertension, hypokalaemia and fluid retention (see section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see section 5.1). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on digoxin), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular dysrhythmia and those with severe renal impairment).

Blood pressure, serum potassium and fluid retention should be monitored at least once a month.

TERONRED 250 should be used with caution in patients with a history of cardiovascular disease. The safety of TERONRED 250 in patients with left ventricular ejection fraction measurement of < 50 % or NYHA Class II to IV heart failure has not been established. Before treating patients with TERONRED 250, hypertension must be

controlled and hypokalaemia corrected.

Before treating patients with a significant risk for congestive heart failure (e.g. a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with TERONRED 250, cardiac failure should be treated and cardiac function optimised.

Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with TERONRED 250 treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function.

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase and bilirubin levels should be measured prior to starting treatment with TERONRED 250, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, ALT (alanine aminotransferase) or AST (aspartate aminotransferase), should be measured immediately. If at any time the ALT or AST rises above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with TERONRED 250 should be interrupted immediately and liver function closely monitored.

Re-treatment with TERONRED 250 may take place only after liver function tests return

to the patient's baseline and at a reduced dose level (see section 4.2).

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, TERONRED 250 should be discontinued and patients should not be re-treated with TERONRED 250.

There are no data to support the use of TERONRED 250 in patients with active or symptomatic viral hepatitis.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). TERONRED 250 should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

There have been post-marketing reports of acute liver failure and fulminant hepatitis, some with fatal outcome (see section 4.8).

Risk of non-alcoholic fatty liver disease (NAFLD)

Testosterone deficiency is associated with higher serum and hepatic levels of triglycerides and higher serum levels of low-density lipoprotein (LDL) in the body, with significant increases in fasting plasma glucose and insulin levels. Patients who receive androgen deprivation therapy (ADT) are at a greater risk of being diagnosed with NAFLD.

ADT is also associated with significant increase in incidences of other liver diseases such as cirrhosis, liver necrosis, and any liver disease. A significant correlation between the number of ADT doses and the incidence of NAFLD and other liver diseases has been noted.

Normal androgen levels prevent hepatic fat accumulation, whereas androgen deficiency induces hepatic steatosis.

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if

patients are withdrawn from prednisone or prednisolone. If TERONRED 250 is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see "Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess" above).

In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of TERONRED 250 in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole

Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Hypoglycaemia

Cases of hypoglycaemia have been reported when abiraterone as in TERONRED 250 plus prednisone / prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide

(see section 4.5). Blood glucose should be monitored in patients with diabetes.

Vaccination with live attentuated bacterial or viral vaccines

Prostate cancer patients on treatment should receive guidance on age and indication appropriate vaccinations, in particular live attentuated bacterial or viral vaccines. Patients should also be advised to take extra precaution should they come into contact

with someone who has received a live vaccine.

Tuberculosis and/or HIV

Prostate cancer patients with tuberculosis and/or HIV, who are not well-controlled on treatment should be monitored closely.

Use with chemotherapy

The safety and efficacy of concomitant use of TERONRED 250 with cytotoxic chemotherapy has not been established.

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with TERONRED 250. Most cases developed within the first 6 months of treatment and recovered after TERONRED 250 was withdrawn. Caution should be exercised in patients concomitantly treated with medicines known to be associated with myopathy/rhabdomyolysis.

Potential risks

Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with TERONRED 250.

Interactions with other medicines

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223

Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.

It is recommended that subsequent treatment with Ra-223 is not initiated for at least 5

days after the last administration of TERONRED 250 in combination with prednisone/prednisolone.

Excipients warnings

TERONRED 250 contains lactose. Patients with the rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take TERONRED 250.

This medicine contains 25,52 mg sodium per daily dose of four TERONRED 250 tablets, equivalent to 1,28 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Effect of food on TERONRED 250

Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety when given with food have not been established therefore TERONRED 250 must not be taken with food (see sections 4.2 and 5.2).

Interactions with other medicines

Potential for other medicines to affect abiraterone exposures

It was reported that in a clinical pharmacokinetic interaction study of healthy subjects pre-treated with a strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55 % (see section 4.3).

Other strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbitone, St John's Wort [*Hypericum perforatum*]) are to be avoided during treatment with TERONRED 250.

It was reported that in a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no

clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential for TERONRED 250 to affect exposures to other medicines

Abiraterone is an inhibitor of the hepatic medicine-metabolising enzymes CYP2D6 and CYP2C8.

It was reported that in a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2,9-fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33 %.

Caution is advised when administering with medicines activated by or metabolised by CYP2D6, particularly with medicines that have a narrow therapeutic index. Dose reduction of medicines with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicines metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicines requiring CYP2D6 to form their active analgesic metabolites).

It was reported that in a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

It was reported that in a CYP2C8 interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46 % and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10 % when pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with TERONRED 250.

Examples of medicines metabolised by CYP2C8 include pioglitazone and repaglinide

(see section 4.4 Hypoglycaemia).

It was reported that *in vitro*, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicines eliminated by OATP1B1. There are no clinical data available to confirm transporter-based interaction.

Use with medicines known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering TERONRED 250 with medicines known to prolong the QT interval or medicines able to induce *Torsade de pointes* such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc.

Concomitant use with Spironolactone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with TERONRED 250 is not recommended.

Concomitant use with eplenerone

There is no clinical study data related to concomitant use of eplenerone with TERONRED 250.

4.6 Fertility, pregnancy and lactation

Women should not use TERONRED 250.

Women of childbearing potential:

There are no human data on the use of TERONRED 250 in pregnancy and TERONRED 250 is not for use in women of childbearing potential.

Maternal use of a CYP 17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus.

Contraception in males and females:

Studies in animals have shown reproductive toxicity.

It is not known whether abiraterone or its metabolites are present in semen.

During treatment and for 3 months following the last dose of TERONRED 250, patients who engage in sexual activity with pregnant women must use a condom.

If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method until 3 months after the last dose of TERONRED 250.

Female sexual partners (of childbearing potential) of male patients receiving TERONRED 250, should be advised to use highly effective contraception, during treatment and for 6 months after the last dose of TERONRED 250.

Men should be advised not to father a child while receiving treatment and must use highly effective contraception during treatment and for at least 3 months after treatment.

Pregnancy:

TERONRED 250 is contraindicated in women who are or may potentially be pregnant (see section 4.3).

Pregnant women or women of child-bearing potential should handle TERONRED 250 uncoated tablets with gloves.

Breastfeeding:

TERONRED 250 is not for use in women. It is not known if abiraterone acetate or its metabolites are excreted in human breast milk.

Fertility:

In fertility studies in both male and female rats, abiraterone reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped (see section 5.3).

It is recommended to store semen before starting treatment with TERONRED 250 in patients who might want to father a child.

4.7 Effects on ability to drive and use machines

TERONRED 250 may affect the ability of patients to drive or use machines. Patients should not drive and use machines before they know how treatment with TERONRED 250 affects their ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and increased alanine aminotransferase and/or increased aspartate aminotransferase. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis. Hypertension, hypokalaemia and fluid retention may occur as a pharmacodynamic consequence of the mechanism of action of abiraterone acetate. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

Tabulated list of adverse reactions

Table 1: The following undesirable effects have been observed and reported during treatment with abiraterone acetate as in TERONRED 250:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: Frequent, Less Frequent and Frequency unknown. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations	urinary tract infection, sepsis		
Immune system disorders			Anaphylactic reaction

Endocrine disorders		adrenal insufficiency	
Metabolism and nutrition disorders	hypokalaemia, hypertriglyceridaemia		
Cardiac disorders	cardiac failure (includes congestive heart failure, left ventricular dysfunction and decreased left ventricular ejection fraction), angina pectoris, atrial fibrillation, tachycardia	dysrhythmia	myocardial infarction, QT prolongation
Vascular disorders	hypertension		
Respiratory, thoracic and mediastinal disorders		allergic alveolitis	
Gastrointestinal disorders	diarrhoea, dyspepsia		
Hepatobiliary disorders	Hepatotoxicity, abnormal hepatic functions including elevated hepatic	hepatitis fulminant, acute hepatic failure	non-alcoholic fatty liver disease (NAFLD),

	function tests such as increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and total bilirubin		cirrhosis, liver necrosis
Skin and subcutaneous tissue disorders	rash		
Musculoskeletal and connective tissue disorders	fractures (includes osteoporosis and all fractures with the exception of pathological fractures)	myopathy, rhabdomyolysis	
Renal and urinary disorders	haematuria	renal failure (secondary to rhabdomyolysis)	
General disorders and administration site conditions	peripheral oedema		

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA

via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, the undesirable effects can be precipitated and/or be of increased severity (see section 4.8). There is no specific antidote. Treatment with TERONRED 250 must be discontinued. Treatment is symptomatic and supportive which includes relevant monitoring of cardiac and hepatic function, serum potassium and blood pressure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A21.12 Hormone inhibitors

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see section 4.4).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH (luteinizing hormone releasing hormone) analogues or orchiectomy, decrease

androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. PSA serves as a biomarker in patients with prostate cancer. It was reported that in a Phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 38 % of patients treated with abiraterone acetate, versus 10 % of patients treated with placebo, had at least a 50 % decline from baseline in PSA levels.

5.2 Pharmacokinetic properties

It was reported that following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see section 5.1).

Absorption

The time to reach maximum plasma abiraterone concentration in the fasting state is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the

potential to result in highly variable exposures. Therefore, **abiraterone acetate must not be taken with food**. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone acetate. The tablets should be swallowed whole with water (see section 4.2).

Distribution

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99,8 %. The apparent volume of distribution is approximately 5 630 ℓ, implying that abiraterone is extensively distributed to peripheral tissues.

Biotransformation

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92 %) is found in the form of metabolites of abiraterone. Abiraterone sulphate and N-oxide abiraterone sulphate are 2 main metabolites of the 15 detectable metabolites, each representing approximately 43 % of total radioactivity.

Elimination

Based on data from healthy subjects, the mean half-life of abiraterone in plasma is approximately 15 hours. Following oral administration of ^{14}C-abiraterone acetate 1000 mg, approximately 88 % of the radioactive dose is recovered in faeces and approximately 5 % in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55 % and 22 % of the administered dose, respectively).

Patients with hepatic impairment

The pharmacokinetics of abiraterone acetate was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral

dose of 1 000 mg increased by approximately 11 % and 260 % in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. Abiraterone acetate should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see sections 4.2 and 4.4).

Patients with renal impairment

The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1 000 mg dose did not increase in subjects with end-stage renal disease on dialysis. Patients with renal impairment, including severe renal impairment, do not require dose reduction (see section 4.2).

5.3 Preclinical safety data

In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the

pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced foetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Environmental Risk Assessment (ERA)

The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulphate

Film-coat:

Opadry white

Opadry white consists of:

Hypromellose

Macrogol

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep containers well closed.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

TERONRED 250 film-coated tablets are available in high density polyethylene (HDPE) containers along with an oxygen absorbent pillow pouch in a pack size of 120**.**

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering TERONRED 250

Based on its mechanism of action, TERONRED 250 may harm a developing foetus.

Women (including healthcare providers) who are pregnant or women who may be pregnant should not handle TERONRED 250 without protection e.g. gloves (see section 4.6).

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements. This medicine may pose a risk to the aquatic environment (see section 5.3).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

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8. REGISTRATION NUMBER(S)

51/21.12/0732

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 September 2020

10 DATE OF REVISION OF TEXT

28 March 2025