APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TERONRED 500 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg abiraterone acetate.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each film-coated tablet contains 245 mg of lactose monohydrate and

11,69 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Purple coloured, oval shaped, biconvex bevel edged film-coated tablets, debossed with "A" on one side and "500" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERONRED 500 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 500 is 1 g (two 500 mg tablets) as a single daily dose that **must not be taken with food**. Taking TERONRED 500 with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Patients should be maintained on TERONRED 500 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 500 is used with 5 mg prednisone or prednisolone once daily.

For metastatic castration-resistant prostate cancer (mCRPC), TERONRED 500 is used with 10 mg prednisone or prednisolone daily.

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with TERONRED 500, 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 missed daily dose of either TERONRED 500, 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 500 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 500 (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 normalise (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 (one tablet) 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 500 should be discontinued and patients should not be re-treated with TERONRED 500.

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 500 in paediatric patients, as prostate cancer is not present in the paediatric population.

Method of administration:

TERONRED 500 is for oral use.

TERONRED 500 must be taken on an empty stomach, at least one hour before or at least two hours after a meal.

TERONRED 500 tablets should be swallowed whole with water.

Precautions to be taken before handling or administering TERONRED 500

Based on its mechanism of action, TERONRED 500 may cause harm to a developing foetus; therefore women (including healthcare professionals), who are pregnant or who may be pregnant should not handle TERONRED 500 without protection e.g., gloves (see sections 4.6 and 6.6).

4.3 Contraindications

TERONRED 500 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 500.
- 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 500 with prednisone or prednisolone is contraindicated in combination with Ra-223 (radium 223).

4.4 Special warnings and precautions for use

<u>Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess</u>

TERONRED 500 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 cardiac glycosides), 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 500 should be used with caution in patients with a history of cardiovascular disease. The safety of TERONRED 500 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 500, 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 500, 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 500 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 (see section 4.2).

<u>Hepatotoxicity and hepatic impairment</u>

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 500, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, 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 500 should be interrupted immediately and liver function closely monitored.

Re-treatment with TERONRED 500 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 500 should be permanently discontinued and patients should not be re-treated with TERONRED 500.

There are no data to support the use of TERONRED 500 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 500 should not be used in patients with moderate to severe hepatic impairment (see sections 4.2, 4.3, 5.2).

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 500 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 500 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 500 plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar 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 500 with cytotoxic chemotherapy has not been established.

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with abiraterone. Most cases developed within the first 6 months of treatment and recovered after abiraterone 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 500.

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 studies.

It is recommended that subsequent treatment with Ra-223 is not initiated for at least 5 days after the last administration of TERONRED 500 in combination with prednisone/prednisolone.

Excipients warnings

TERONRED 500 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TERONRED 500.

TERONRED 500 also contains sodium. 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 500

Administration of TERONRED 500 with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of TERONRED 500 when given with food have not been established. **TERONRED 500 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, rifampicin,

rifabutin, rifapentine, phenobarbitone, St John's Wort [*Hypericum perforatum*]) are to be avoided during treatment with TERONRED 500.

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 500 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 clinical 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 by approximately 200 %. 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 500. 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 500 with medicines known to prolong the QT interval or medicines able to induce *Torsades 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 500 is not recommended.

Concomitant use with eplenerone

There is no clinical study data related to concomitant use of eplenerone with TERONRED 500.

4.6 Fertility, pregnancy and lactation

Women should not use TERONRED 500.

<u>Women of childbearing potential:</u>

There are no human data on the use of TERONRED 500 in pregnancy and TERONRED 500 is not for use in women of childbearing potential.

Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus.

Contraception in males and females:

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 500, 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 500.

Female sexual partners (of childbearing potential) of male patients receiving TERONRED 500, should be advised to use highly effective contraception, during treatment and for 6 months after the last dose of TERONRED 500.

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 500 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 500 tablets with gloves.

Breastfeeding:

TERONRED 500 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.

It is recommended to store semen before starting treatment with TERONRED 500 in patients who might want to father a child.

4.7 Effects on ability to drive and use machines

TERONRED 500 has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

Table 1: The following undesirable effects have been observed and reported during treatment with abiraterone acetate as in TERONRED 500:

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations	urinary tract infection, sepsis		
Immune system disorders			Ana-phylactic reactions
Endocrine disorders		adrenal insufficiency	
Metabolism and nutrition disorders	hypokalaemia, hypertriglyceridaemia		
Cardiac disorders	cardiac failure (includes congestive heart failure,	Other dysrhythmias	myocardial infarction, QT

	left ventricular dysfunction and ejection fraction decreased), angina pectoris, atrial fibrillation, tachycardia		prolongation
Vascular disorders	hypertension		
Respiratory, thoracic and mediastinal disorders		allergic alveolitis	
Gastrointestinal disorders	diarrhoea, dyspepsia		
Hepatobiliary disorders	Hepatotoxicity, abnormal hepatic functions including elevated hepatic function tests such as increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and total bilirubin	hepatitis fulminant, acute hepatic failure	non-alcoholic fatty liver disease (NAFLD), cirrhosis, liver necrosis
Skin and	rash		

subcutaneous tissue disorders			
Musculoskeletal and connective tissue disorders	fractures (includes osteoporosis and all fractures with the exception of pathological fractures)	myopathy, rhabdomyolysis	
Renal and urinary disorders	haematuria		
General disorders and administration site conditions	peripheral oedema		

The following Grade 3 adverse reactions occurred in patients treated with abiraterone acetate: hypokalaemia 5 %; urinary tract infection 2 %; alanine aminotransferase increased and/or aspartate aminotransferase increased 4 %; hypertension 6 %; fractures 2 %; peripheral oedema, cardiac failure, and atrial fibrillation 1 % each. Grade 3 hypertriglyceridaemia and angina pectoris occurred in < 1 % of patients. Grade 4 urinary tract infection, alanine aminotransferase increased and/or aspartate aminotransferase increased, hypokalaemia, cardiac failure, atrial fibrillation, and fractures occurred in < 1 % of patients.

A higher incidence of hypertension and hypokalaemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36,7 % of patients in the hormone sensitive population (study 3011) compared to 11,8 % and 20,2 % in studies 301 and 302, respectively. Hypokalaemia was observed in 20,4 % of patients in the hormone sensitive population (study 3011) compared to 19,2 % and 14,9 % in

301 and 302, respectively).

The incidence and severity of adverse events was higher in the subgroup of patients with baseline ECOG2 performance status grade and also in elderly patients (≥ 75 years).

Description of selected adverse reactions

Cardiovascular reactions

Three Phase 3 studies conducted with abiraterone acetate excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50 %. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2,6 % vs. 2,0 %, tachycardia 1,9 % vs. 1,0 %, angina pectoris 1,7 % vs. 0,8 %, cardiac failure 0,7 % vs. 0,2 %, and arrhythmia 0,7 % vs. 0,5 %.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g. ALT or AST increases of > 5 x ULN or bilirubin increases > 1,5 x ULN) were reported in approximately 6 % of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In

Study 3011, grade 3 or 4 hepatotoxicity was observed in 8,4 % of patients treated with abiraterone acetate. Ten patients who received abiraterone acetate were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6,5 %) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate).
In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1,1 % of patients treated with abiraterone acetate and 0,6 % of patients treated with placebo; no deaths were reported due to hepatotoxicity events.
In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2,5 X ULN, bilirubin > 1,5 X ULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were excluded. In the 301 trial, patients

with baseline ALT and AST ≥ 2,5 x ULN in the absence of liver metastases and > 5 x ULN in the presence of liver metastases were excluded. In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2,5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see section 4.2). Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

<u>Reporting of suspected adverse reactions</u>

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.

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4.9 Overdose

There is no specific antidote. In the event of an overdose, administration of TERONRED 500 should be stopped and general supportive measures undertaken, including monitoring for dysrhythmias. Liver function should also be assessed. In cases of overdose, side effects may be exacerbated and exaggerated.

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 luteinising hormone-releasing hormone (LHRH) agonists 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 agonists (or orchiectomy).

Pharmacodynamic effects

Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. 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

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

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours. Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 17-fold 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 TERONRED 500 with meals has the potential to result in highly variable exposures. Therefore, **TERONRED 500 must not be taken with food.**

TERONRED 500 must be taken at least two hours after eating and food must not be eaten for at least one hour after taking TERONRED 500. The tablets must 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, suggesting that abiraterone is extensively distributed to peripheral tissues.

Metabolism

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.

Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents 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 with abiraterone acetate, 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 a dose reduction of abiraterone acetate (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose (silicified)

Sodium lauryl sulphate

Film-coat:

Opadry II Purple

Opadry II Purple consists of:

Ferrosoferric Oxide / Black Iron Oxide

Iron Oxide Red

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, Protect from light.

Keep containers well closed.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

TERONRED 500 film-coated tablets –

60 tablets are packed in 120cc HDPE round, white opaque bottles with 38 mm child resistance closure with heat seal and pulp liner for induction seal.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering TERONRED 500

Based on its mechanism of action, TERONRED 500 may harm a developing foetus. Women (including healthcare providers) who are pregnant or women who may be pregnant should not handle TERONRED 500 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

South Africa.

Tel.: +27 11 324 2100

8. REGISTRATION NUMBER(S)

56/21.12/0715

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2023

10. DATE OF REVISION OF TEXT

10 March 2025