PROFESSIONAL INFORMATION FOR PROTYGA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PROTYGA 250 mg uncoated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg abiraterone acetate.

Contains sugar (lactose monohydrate, 150 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PROTYGA tablets are white to off-white, oval shaped tablets, debossed with “A” on one side and “250” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROTYGA 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 **PROTYGA** is 1 g (four 250 mg tablets) as a single daily dose that **must not be taken with food**.

Taking **PROTYGA** with food increases systemic exposure to abiraterone (see section 4.5 and 5.2).

Patients should be maintained on **PROTYGA** 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), **PROTYGA** is used with 5 mg prednisone or prednisolone once daily.

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

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with **PROTYGA**, 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 **PROTYGA**, 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 **PROTYGA** when administered to patients with moderate or severe hepatic impairment (Child- Pugh class B or C). No dose adjustment can be predicted.

PROTYGA should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment with **PROTYGA** (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases above 5 times the upper limit of normal 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 the first 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, **PROTYGA** should be discontinued and patients should not be re-treated with **PROTYGA**.

Renal impairment

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

Paediatric population

There is no relevant use of **PROTYGA** in paediatric patients, as prostate cancer is not present in the paediatric population.

Method of administration

PROTYGA is for oral use.

PROTYGA should be taken on an empty stomach, at least one hour before or at least two hours after a meal.

The tablets should be swallowed whole with water.

For precautions to be taken before handling or administering **PROTYGA**, see section 6.6.

Women who are or may be pregnant should not handle **PROTYGA** without gloves.

4.3 Contraindications

PROTYGA is contraindicated in:

- Patients with hypersensitivity to abiraterone or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment (Child-Pugh class B and C) (see section 4.2, 4.4 and 5.2).
- Women should not use **PROTYGA.**
- Women who are pregnant, trying to get pregnant or may potentially be pregnant (see section 4.6).
- Concomitant administration with rifampicin (see section 4.5).
- **PROTYGA** with prednisone or prednisolone is contraindicated in combination with Radium 223.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess

PROTYGA 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). Concomitant use of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions.

PROTYGA should be used with caution in patients with a history of cardiovascular disease. The safety of **PROTYGA** in patients with left ventricular ejection fraction < 50 % or New York Heart Association (NYHA) class III or IV heart failure has not been established. Hypertension must be controlled and hypokalaemia must be corrected, before treatment with **PROTYGA**.

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 monthly.

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 **PROTYGA**, 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 **PROTYGA** 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).

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes have led to **PROTYGA** discontinuation or dose modification. Serum transaminase and bilirubin levels should be measured prior to starting treatment with **PROTYGA**, every two weeks for the first three months of treatment, and monthly thereafter. If clinical signs and symptoms suggestive of hepatotoxicity develop, serum transaminases, should be measured immediately.

If at any time ALT or AST rises above 5 times the upper limit of normal or bilirubin rises above 3 times the upper limit of normal, treatment with **PROTYGA** should be stopped immediately and the liver function should be monitored closely.

Re-treatment with **PROTYGA** may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see section 4.2).

PROTYGA should be discontinued if patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while taking **PROTYGA**.
These patients should not be re-treated with **PROTYGA**.

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

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

Acute liver failure and fulminant hepatitis, some with fatal outcome have been reported (see section 4.8).

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 therapy.
If **PROTYGA** is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.
In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage of corticosteroids may be indicated before, during and after the stressful situation.

Use with chemotherapy

The safety and efficacy of concomitant use of **PROTYGA** with cytotoxic chemotherapy have not been established.

Use in combination with Radium 223

Treatment with **PROTYGA** and prednisone/prednisolone in combination with Radium 223 is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased mortality. It is recommended that subsequent treatment with Radium 223 is not initiated for at least 5 days after the last administration of **PROTYGA** in combination with prednisone/prednisolone.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of **PROTYGA** 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.

Potential risks

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

Skeletal muscle effects

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

Caution is recommended in patients concomitantly treated with medicines known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic

alternative, due to risk of decreased exposure to **PROTYGA** (see section 4.5).

Excipient warnings

PROTYGA contains lactose monohydrate (see section 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **PROTYGA**.

PROTYGA also contains 80 mg sodium per daily dose, equivalent to approximately 4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should 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 PROTYGA

The absorption of abiraterone acetate, as in **PROTYGA**, significantly increases when taken with food. The safety and efficacy of **PROTYGA** when given with food have not been established. **PROTYGA** must not be taken with food (see section 4.2 and 5.2).

Interactions with other medicines

*Potential for **PROTYGA** to affect exposure to other medicines:*

Abiraterone, as in **PROTYGA**, is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.

Caution is advised when **PROTYGA** is administered with medicines activated by or metabolised by CYP2D6, particularly with medicines that have a narrow therapeutic index. Dose reduction of narrow therapeutic index medicines metabolised by CYP2D6 should be considered (e.g. paroxetine propafenone, flecainide, haloperidol, metoprolol, propranolol, venlafaxine, risperidone, codeine, oxycodone and tramadol).

Although no meaningful increases in exposure are expected when **PROTYGA** is combined with medicines that are predominantly eliminated by CYP2C8, patients should be monitored for signs of

toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.

*Potential for other medicines to affect **PROTYGA** exposures:*

Rifampicin, a strong inducer of CYP3A4, decreases the mean plasma AUC of abiraterone, as contained in **PROTYGA**, by 55 % (see section 4.3).

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

Co-administration of ketoconazole, a strong inhibitor of CYP3A4, has no clinically meaningful effect on the pharmacokinetics of abiraterone.

Concomitant use with medicines known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering **PROTYGA** 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) 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 **PROTYGA** is not recommended.

Concomitant use with eplerenone

There is no data available on the concomitant use of eplerenone with **PROTYGA**.

4.6 Fertility, pregnancy and lactation

Women should not use **PROTYGA**.

Pregnancy

PROTYGA is contraindicated in pregnant or potentially pregnant women (see section 4.3).

Pregnant women or women of child-bearing potential should handle **PROTYGA** with gloves (see section 6.6).

Women of childbearing potential

PROTYGA is not indicated for use in women of childbearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect the development of the foetus.

Contraception in males and females

Animal studies have shown reproductive toxicity.

The presence of **PROTYGA** or its metabolites in semen is unknown. If patient on treatment with **PROTYGA** is engaged in sexual activity with a pregnant woman, a condom is required. If the patient is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method until one week after the last dose of **PROTYGA**.

Fertility

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone, as in **PROTYGA**, was stopped. It is recommended to store semen before starting treatment with **PROTYGA** in patients who might want to father a child.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

PROTYGA may affect the ability to drive or use machines. Patients should not drive and use machines before they know how treatment with **PROTYGA** affects their ability to drive and use machines.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Urinary tract infection, sepsis
Endocrine disorders	Less frequent	Adrenal insufficiency
Metabolism and nutrition disorders	Frequent	Hypokalaemia, hypertriglyceridaemia
Cardiac disorders	Frequent Less frequent Frequency unknown	Cardiac failure (including congestive heart failure, left ventricular dysfunction and decreased left ventricular ejection fraction), angina pectoris, atrial fibrillation, tachycardia Cardiac dysrhythmias Myocardial infarction, QT prolongation
Vascular disorders	Frequent	Hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Allergic alveolitis
Gastrointestinal disorders	Frequent	Diarrhoea, dyspepsia
Hepato-biliary disorders	Frequent Less frequent	Hepatotoxicity, abnormal hepatic functions, including elevated hepatic function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin. Hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Rash

Musculoskeletal, and connective tissue disorders	Frequent Less frequent	Fractures (including osteoporosis and all fractures with the exception of pathological fracture) Myopathy, rhabdomyolysis
Renal and urinary disorders	Frequent Less frequent	Haematuria Renal failure secondary to rhabdomyolysis
General disorders and administration site conditions	Frequent	Peripheral oedema
Injury, poisoning and procedural complications	Frequent	Fractures (includes osteoporosis and all fractures with the exception of pathological fractures)

Reporting of suspected adverse reactions:

Reporting of 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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 **PROTYGA** 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

A 21.12 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. Specifically, 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 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).

Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In patients who failed prior chemotherapy with taxanes, some patients treated with abiraterone acetate had at least a 50 % decline from baseline in PSA levels.

5.2 Pharmacokinetic properties

Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see section 5.1).

Absorption

Maximum plasma abiraterone concentration is reached approximately 2 hours after oral administration of abiraterone acetate (fasting state).

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 abiraterone acetate with meals has the potential to result in highly variable exposures. Therefore, **abiraterone acetate must not be taken with food**. Abiraterone acetate tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone acetate tablets. 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 about 5 630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

After oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone. Abiraterone 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. There are 15 detectable metabolites.

Two main metabolites, abiraterone sulphate and *N*-oxide abiraterone sulphate, each represent about 43 % of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. After oral administration of ^{14}C-abiraterone acetate 1 g, 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 (about 55 % of the administered dose) and abiraterone (about 22 % of the administered dose).

Patients with hepatic impairment

After a single oral 1 g dose, the systemic exposure to abiraterone increases by approximately 11 % and 260 % in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to about 18 hours in patients with mild hepatic impairment and to about 19 hours in patients with moderate 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 section 4.2 and 4.4).

Patients with renal impairment

After a single oral 1 g dose the systemic exposure to abiraterone does not increase in patients with end-stage renal disease on dialysis. No dose adjustment is necessary for patients with renal impairment, including severe renal impairment (see section 4.2).

5.3 Preclinical safety data

In all animal toxicity studies, circulating testosterone levels are 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 are observed. All changes show 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 reverse or resolve 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 are 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

HDPE round opaque white/off-white bottles with 38 mm child resistance closure with heat seal and pulp liner for induction seal.

Pack size: 120 tablets.

6.6 Special precautions for disposal and handling

Precautions to be taken before handling or administering PROTYGA:

Based on its mechanism of action, **PROTYGA** may harm a developing foetus: therefore, women (including health care providers) who are pregnant or women who may be pregnant, should not handle **PROTYGA** 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

13 Pasita Street

Rosen Heights

Rosen Park

Bellville

7530

South Africa

8. REGISTRATION NUMBER

52/21.12/0340

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 June 2020