SCHEDULING STATUS

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1. NAME OF THE MEDICINE

ABITIG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg abiraterone acetate.

Excipients with known effect:

Contains sugar (164,75 mg lactose monohydrate per tablet).

Contains sodium (4,6 mg sodium per tablet - 18,4 mg sodium per daily dose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, oval, biconvex, uncoated tablet debossed with “993” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABITIG 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;

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(2) Presence of 3 or more bone lesions;

(3) Presence of measurable visceral (excluding lymph node disease) metastasis.

- The treatment of patients with metastatic castration-resistant prostate cancer with bone metastases are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- The treatment of patients with metastatic advanced prostate cancer (castration-resistant prostate cancer) who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

ABITIG **should** be prescribed by a medical practitioner qualified in the use of anti-cancer chemotherapy.

Posology

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

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

Dosage for prednisone or prednisolone

For metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate cancer (mHSPC), ABITIG is used with 5 mg prednisone or prednisolone once daily.

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

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Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with ABITIG 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 ABITIG, 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 ABITIG when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. ABITIG should not be used in patients with moderate to severe hepatic impairment (see section 4.3).
For patients who develop hepatotoxicity during treatment with ABITIG (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 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, ABITIG should be discontinued and patients should be re-treated with ABITIG.

Renal impairment

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

Paediatric population

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

Method of administration

ABITIG is for oral use.

ABITIG should be taken on an empty stomach, at least two hours after eating and no food should be eaten for at least one hour after taking ABITIG. The tablets should be swallowed whole with water.

Precautions to be taken before handling or administering ABITIG

Based on its mechanism of action, ABITIG may harm a developing fetus. Women (including health care providers) who are pregnant or women who may be pregnant should not handle ABITIG without protection, e.g. gloves (see sections 4.6 and 6.6).

4.3 Contraindications

- Hypersensitivity to abiraterone acetate or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6). Women who are pregnant, trying to get pregnant or may potentially be pregnant.
- Moderate to severe hepatic impairment (Child-Pugh Class B and C) (see section 5.2).
- Women should not use ABITIG.
- 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).

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- ABITIG with prednisone or prednisolone is contraindicated in combination with ^{223}Ra (radium 223).

4.4 Special warnings and precautions for use

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

ABITIG 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 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 (such as those on cardiac glycosides), or fluid retention (such as 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.

ABITIG should be used with caution in patients with a history of cardiovascular disease. The safety of ABITIG in patients with left ventricular ejection fraction < 50 % or NYHA Class III or IV heart failure has not been established.

Before treating patients with ABITIG, hypertension must be controlled, and hypokalaemia corrected.

Before treating patients with a significant risk for congestive heart failure (such as a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (such as echocardiogram). Before treatment with ABITIG, cardiac failure should be treated, and cardiac function should be optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral

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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 ABITIG 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, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), 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 should be interrupted immediately, and liver function closely monitored.

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

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on ABITIG, treatment should be discontinued, and patients should not be re-treated.

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

There are no data on the clinical safety and efficacy of multiple doses of ABITIG when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). ABITIG should not be used in patients with moderate to severe hepatic impairment (see sections 4.2 and 4.3).

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

It has been reported that 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. Patient's receiving androgen deprivation therapy (ADT) are at a greater risk of being diagnosed with non-alcoholic fatty liver disease (NAFLD) and to show significant increase and/or incidences of liver disease such as cirrhosis and liver necrosis. As Abiraterone is commonly used in conjunction with ADT (see section 4.1), the same can be expected.

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 ABITIG is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information 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 ABITIG in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole

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

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Hyperglycaemia

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

Use with chemotherapy

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

Potential risks

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

Interactions with other medicines

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

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with ABITIG. Most cases developed within the first 6 months of treatment and recovered after ABITIG withdrawal. Caution is recommended in patients concomitantly treated with medicines known to be associated with myopathy/rhabdomyolysis.

Combination of abiraterone and prednisone/prednisolone with radium (^{223}Ra)

Treatment with abiraterone and prednisone/prednisolone in combination with ^{223}Ra increases the risk of fractures and there is a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials. It is recommended that

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subsequent treatment with ^{223}Ra is not initiated for at least 5 days after the last administration of ABITIG in combination with prednisone/prednisolone.

Excipients warnings

ABITIG contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take ABITIG.

ABITIG also contains sodium (4,6 mg sodium per tablet - 18,4 mg sodium per daily dose). 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 ABITIG

Administration with food significantly increases the absorption of ABITIG. The efficacy and safety when given with food have not been established, therefore ABITIG 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 pretreated with a strong CYP3A4 inducer, rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1 000 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, phenobarbital, St John's wort (*Hypericum perforatum*)) during treatment with ABITIG are to be avoided.

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It was reported 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 pharmacokinetic properties of abiraterone, as in ABITIG.

Potential 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 by 33 %.

Caution is advised when administering ABITIG 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 CYP1A2 substrate theophylline, no increase in systematic 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 1 000 mg abiraterone acetate. When ABITIG 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 with abiraterone as in ABITIG.

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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 products known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ABITIG 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.

Use with spironolactone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ABITIG is not recommended (see section 5.1).

Use with eplenerone

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

4.6 Fertility, pregnancy and lactation

Women should not use ABITIG.

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABITIG. If the patient becomes pregnant while receiving ABITIG, the potential

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hazard to the foetus must be explained. An effective method of contraception should be used during treatment and for 6 months after the last dose of ABITIG.

Contraception in males and females

Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of Abiraterone acetate.

Pregnancy

ABITIG is not indicated for use in women and is contraindicated in women who are or may potentially be pregnant (see section 4.3 and 5.3).

Pregnant women or women of childbearing potential should handle ABITIG with gloves.

Breastfeeding

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

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 ABITIG, was stopped. It is recommended to store semen before starting treatment with ABITIG in patients who might want to father a child.

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4.7 Effects on ability to drive and use machines

ABITIG may affect the ability of patients to drive or use machines.

Patients should not drive or use machines before they know how treatment with ABITIG affects their ability to drive and use machines.

4.8 Undesirable 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 cardiac failure, (including congestive heart failure, left ventricular dysfunction and decreased left ventricular ejection fraction), angina pectoris, atrial fibrillation, tachycardia, cardiac dysrhythmias

Frequency unknown myocardial infarction, QT prolongation

Vascular disorders

Frequent hypertension

Respiratory, thoracic and mediastinal disorders

Less frequent allergic alveolitis

Gastrointestinal disorders

Frequent diarrhoea, dyspepsia

Hepatobiliary disorders

Frequent hepatotoxicity, abnormal hepatic functions including elevated hepatic function tests such as increased alanine aminotransferase (ALT) and/or

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	increased aspartate aminotransferase (AST), and total bilirubin
Less frequent	fulminant hepatitis, acute hepatic failure, cirrhosis, liver necrosis

Skin and subcutaneous tissue disorders

Frequent	rash

Musculoskeletal and connective tissue disorders

Frequent	fractures (includes osteoporosis and all fractures with the exception of pathological fractures)
Less frequent	myopathy, rhabdomyolysis

Renal and urinary disorders

Frequent	haematuria
Less frequent	renal failure (secondary to rhabdomyolysis)

General disorders and administration site conditions

Frequent	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

There is no specific antidote. In the event of an overdose, administration should be withheld, and general supportive measures undertaken, including monitoring for dysrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function should also be assessed. In overdose, the undesirable effects can be precipitated and/or be of increased severity (see section 4.8).

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: 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, dehydroepiandrosterone (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) 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 acetate decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis.

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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.

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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

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 10-fold (AUC) and 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 one hour before or at least two hours after eating.

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, suggesting that abiraterone extensively distributes 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,

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hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92 %) is found in the form of metabolites of abiraterone. Of the15 detectable metabolites, 2 main metabolites, abiraterone sulphate and *N*-oxide abiraterone sulphate, each represents approximately 43 % of the total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of 1 g ^{14}C-abiraterone acetate, 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).

Special populations

Hepatic impairment

The pharmacokinetic properties 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 1 g dose 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.

During pharmacokinetic studies, the AUC of abiraterone increased by approximately 600 % and the fraction of free medicine increased by 80 % in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.

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There are no data on 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).

Renal impairment

It was reported that the pharmacokinetic properties of abiraterone acetate were 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 g dose did not increase in subjects with end-stage renal disease on dialysis. Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxyanisole

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium laurilsulfate

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6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

Keep in the original bottle until required for use.

6.5 Nature and contents of container

White, round, high density polyethylene bottle with a white, polypropylene cap.

Pack size: 120 tablets.

6.6 Special precautions for disposal and other handling

Based on its mechanism of action, ABITIG may harm a developing fetus. Therefore, women who are pregnant or may be pregnant, including health care workers, should not handle ABITIG without protection, such as gloves (see section 4.6).

Any unused product or waste material should be disposed of in accordance with local requirements. ABITIG may pose a risk to the aquatic environment (see section 5.3).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd - Roodepoort

14 Lautre Road

Stormill, Ext.1, Roodepoort

Signed:

Johannesburg 1724

8. REGISTRATION NUMBER

Abitig: 51/21.12/0508

Abarine: 51/21.12/0509.508

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 June 2021

10. DATE OF REVISION OF THE TEXT

26 November 2024

Signed: