PROFESSIONAL INFORMATION FOR

ABIRATERONE CIPLA (TABLET)

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ABIRATERONE CIPLA

Abiraterone acetate 250 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains abiraterone acetate 250 mg as the active ingredient.

Contains sugar: lactose monohydrate 150 mg per tablet.

For the full list of excipients, **see section 6.1**.

3. PHARMACEUTICAL FORM

White to off-white oval shaped tablets, debossed with "A" on one side and "250" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABIRATERONE CIPLA tablets are indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

Posology:

The recommended dose is 1 g (equivalent to four 250 mg tablets) as a single dose **that must not be taken with food** (see Method of administration below). Taking ABIRATERONE CIPLA with food increases systemic exposure to abiraterone (see **sections 4.5** and **5.2**).

Patients should be maintained on ABIRATERONE CIPLA 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:

ABIRATERONE CIPLA is used with low dose prednisone or prednisolone. The recommended dose of prednisone and prednisolone is 10 mg daily.

Recommended monitoring:

Serum transaminases and bilirubin should be measured prior to initiation of treatment with ABIRATERONE CIPLA, every two weeks in the first three months of treatment and thereafter at least monthly or more frequently if needed. Blood pressure, serum potassium and fluid retention should be monitored at least monthly or more frequently if needed. (see **section 4.4**).

If a patient misses a dose of either ABIRATERONE CIPLA, prednisone or prednisolone, treatment should continue the next day with the usual daily dose.

Special populations

Patients with hepatic impairment:

Dose adjustment is not necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A. ABIRATERONE CIPLA should not be used in patients with pre-existing moderate to severe hepatic impairment, Child-Pugh Class B or C (see **sections 4.3** and **5.2.** For patients who develop hepatotoxicity during treatment with ABIRATERONE CIPLA (alanine aminotransferase ALT) 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 hepatic function tests are back to pre-treatment status (see **section 4.4.**).

Re-treatment following return of hepatic function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients that are being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks in the first three months and thereafter monthly or more frequently if needed. If hepatotoxicity recurs at the reduced daily dose of 500 mg (2 tablets), treatment should be discontinued. Reduced doses should not be taken with food

If patients develop severe hepatotoxicity (ALT 20 times the upper limit of normal) at any time during therapy, treatment should be discontinued, and patients must not be re-treated with ABIRATERONE CIPLA.

Patients with renal impairment:

Dose adjustment is not necessary in patients with renal impairment. (see **section 5.2**)

Paediatric patients:

ABIRATERONE CIPLA is not for use in paediatrics as prostate cancer does not affect children.

Method of administration:

ABIRATERONE CIPLA is for oral use.

ABIRATERONE CIPLA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. The tablets should be swallowed whole with water.

*Precautions to be taken before handling or administering ABIRATERONE CIPLA (see **section 6.6**).*

4.3 Contraindications

ABIRATERONE CIPLA is contraindicated in:

- Patients that are hypersensitive to the active ingredient, abiraterone, or any of the other ingredients of ABIRATERONE CIPLA (see **section 6.1**).
- Women who are pregnant, trying to get pregnant or may potentially be pregnant (see **section 4.6**).

- Patients with moderate to severe hepatic impairment (Child-Pugh class B and C).
- Hypertension not well controlled with appropriate treatment.
- Myocardial infarction and/or arterial thrombotic events in the past 6 months prior to treatment.
- Severe and/or unstable angina pectoris not well controlled with appropriate treatment.
- NYHA class III to IV heart failure not well controlled with appropriate treatment.
- A cardiac left ventricular ejection fraction of < 50 % not improving on appropriate therapy.
- Cardiac dysrhythmias (e.g. atrial fibrillation) not well controlled on appropriate treatment.
- Active or symptomatic viral hepatitis.
- Uncorrected hypokalaemia.
- Vaccination with live attenuated bacterial or viral vaccines.
- Patients with Tuberculosis and/or HIV not well controlled on appropriate treatment.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess:

ABIRATERONE CIPLA should be used with caution in patients with a history of cardiovascular diseases (see **section 4.3**). The safety of ABIRATERONE CIPLA

in patients with left ventricular ejection fraction < 50 % or NYHA Class III or IV heart failure has not been established. Hypertension needs to be controlled and hypokalaemia must be corrected prior to treatment with ABIRATERONE CIPLA.

ABIRATERONE CIPLA can result in hypertension, hypokalaemia and fluid retention (see **sections 4.8 and 5.1**). Co-administration of ABIRATERONE CIPLA with corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive. Caution must be exercised when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia or fluid retention e.g. those with heart failure, recent myocardial infarction or ventricular dysrhythmia (see **section 4.3**). Blood pressure, serum potassium and fluid retention should be monitored at least monthly or more frequently if needed.

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), an assessment of cardiac function (e.g. echocardiogram) must be considered. Cardiac failure should be treated, and cardiac function be optimized prior to treatment with ABIRATERONE CIPLA. Hypertension, hypokalaemia and fluid retention should be corrected and controlled (see **section 4.3**). 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

ABIRATERONE CIPLA 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:

There are reports of elevated hepatic enzymes which led to discontinuation of therapy or dose adjustment (see **section 4.8**). Serum transaminase and bilirubin levels should be measured prior to starting treatment with ABIRATERONE CIPLA, every two weeks for the first three months of treatment, and thereafter once per month or more frequently if needed. If there are signs or symptoms suggestive of development of hepatotoxicity, then serum transaminases and particularly ALT should be measured immediately. If at any time the ALT increases above five times the upper limit of normal or bilirubin level increases above three times the upper limit of normal, treatment with ABIRATERONE CIPLA should be interrupted immediately and hepatic functioning be monitored closely.

Re-treatment with ABIRATERONE CIPLA may resume once the hepatic function tests have returned to the patient's baseline level and at a reduced dose level (see **section 4.2**).

If severe hepatotoxicity occurs (with ALT levels 20 times the upper limit of normal), ABIRATERONE CIPLA treatment should be discontinued, and patients should not be re-treated with ABIRATERONE CIPLA.

There are no data on the clinical safety and efficacy of multiple doses of ABIRATERONE CIPLA when administered to patients with moderate or severe

hepatic impairment (Child-Pugh Class B or C). ABIRATERONE CIPLA should not be used in patients with moderate or severe hepatic impairment (see **sections 4.2, 4.3** and **5.2**).

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

Corticosteroid withdrawal and coverage of stress situations:

Caution should be exercised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. Patients should be monitored for symptoms of mineralocorticoid excess if treatment with ABIRATERONE CIPLA is continued following corticosteroid withdrawal.

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 ABIRATERONE CIPLA 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.

Use with chemotherapy:

The safety and efficacy of concomitant use of ABIRATERONE CIPLA with cytotoxic chemotherapy have not been established (see **section 5.1**).

Potential risks:

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

Skeletal muscle effects:

Cases of myopathy have been reported in patients treated with ABIRATERONE CIPLA. Some patients had rhabdomyolysis with renal failure. Most cases developed within the first month of treatment and recovered after ABIRATERONE CIPLA 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 abiraterone (see **section 4.5**).

Lactose intolerance:

ABIRATERONE CIPLA contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption must not take ABIRATERONE CIPLA.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of food:

Taking ABIRATERONE CIPLA with food increases absorption of abiraterone acetate. The efficacy and safety of ABIRATERONE CIPLA have not been established. Therefore, ABIRATERONE CIPLA must not be taken with food (see **section 4.2**).

Potential for other medicines to affect ABIRATERONE CIPLA:

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 1 000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55 %.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

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

Potential to affect exposures of other medicines:

Abiraterone is an inhibitor of CYP2D6 and CYP2C8 isozymes. In a study to determine the effects of abiraterone acetate (co-administered with prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure of dextromethorphan was increased by approximately 200 %. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased by approximately 33 %.

Therefore, ABIRATERONE CIPLA should be administered with caution with medicines that are activated or metabolised by CYPD26, particularly 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 medicinal products 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).

In a CYP2C8 drug-drug 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

ABIRATERONE CIPLA 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.

In vitro studies have shown that the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were able to inhibit the hepatic uptake transporter OATP1B1 and therefore, 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 ABIRATERONE CIPLA 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 medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with spironolactone:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

There are no human data on the use of ABITARONE CIPLA in pregnancy and ABITARONE CIPLA **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:

Studies have shown reproductive toxicity.

It is not known whether abiraterone acetate and its metabolites are present in semen. Males on treatment with ABIRATERONE CIPLA must use condoms when engaging in sexual activity with women of childbearing age who should use effective contraception and pregnant women who should use a female condom.

Pregnancy:

ABIRATERONE CIPLA is not for use in women and it is contraindicated in pregnant women or those who may potentially be pregnant (see **section 4.3**).

Breastfeeding:

ABIRATERONE CIPLA is not for use in women. It is not known whether abiraterone acetate or its metabolites are excreted in human 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 the abiraterone acetate was stopped (see **section 5.3**).

4.7 Effects on ability to drive and use machines

ABIRATERONE CIPLA may affect the ability of patients to drive or use machines. Patients should not drive and use machines before they know how treatment with ABIRATERONE CIPLA 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, and cardiac dysrhythmias (tachycardia and atrial fibrillation).

Frequency not known: 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 ALT, AST and total bilirubin.

Less frequent: hepatitis fulminant, acute hepatic failure.

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 and rhabdomyolysis.

Renal and urinary disorders:

Frequent: hematuria.

Less frequent: renal failure (secondary to rhabdomyolysis).

General disorders and administrative site disorders:

Frequent: peripheral oedema.

Injury, poisoning and procedural complications:

Frequent: fractures. (includes osteoporosis and all fractures except for pathological fractures).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) :Ltd: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

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 ABIRATERONE CIPLA 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

A21.12 Hormone inhibitors

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

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen-deprivation treatments such as LHRH agonists or orchiectomy, reduce androgen production in the testes but have no effect on androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects:

Abiraterone therapy decreases serum testosterone and other androgens to levels lower than those achieved by LHRH agonists alone or orchiectomy. This results from selective inhibition of CYP17, enzymatic system responsible for biosynthesis

of androgen. 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

Absorption:

Abiraterone takes approximately two hours to reach maximum plasma concentrations following oral administration in the fasting state. When administered with food (as compared to administration under fasting conditions), abiraterone results in up to 10-fold (AUC) and 17-fold (C_{max}) increase in mean systemic exposure, depending on the fat content of the meal.

Given the normal variation in the content and compositions of meals, taking abiraterone with food can result in highly variable plasma exposures. For this reason, abiraterone acetate should not be taken with food. Abiraterone should be taken at least two hours after eating and no food should be taken in the next hour following abiraterone administration. ABIRATERONE CIPLA should be swallowed whole with water (see **section 4.2**).

Distribution:

Abiraterone is 99,8 % bound to plasma proteins in humans. The apparent volume of distribution is approximately 5 630 litres, implying that abiraterone extensively distributes to peripheral tissues.

Biotransformation:

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following 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 and abiraterone (approximately 55 % and 22 % of the administered does, respectively).

Elimination:

Based on data from healthy subjects, the mean half-life of abiraterone in plasma is approximately 15 hours. Following an 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 and abiraterone, representing approximately 55 % and 22 % of the administered dose, respectively.

Patients with hepatic impairment:

Abiraterone acetate pharmacokinetics were studied in patients with pre-existing mild or moderate hepatic impairment, (Child-Pugh class A and B, respectively), as well as in healthy control subjects. Following an oral dose of abiraterone acetate 1 g, systemic exposure was increased by approximately 11 % and 260 % in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is extended to approximately 18 hours in patients with mild hepatic impairment and approximately 19 hours in those with

moderate hepatic impairment. Dose adjustment is not necessary for patients with pre-existing mild hepatic impairment.

Dose adjustment and suspension of treatment may be required for patients who develop hepatotoxicity during abiraterone acetate therapy. Abiraterone acetate should not be used in patients with moderate or severe hepatic impairment (see **sections 4.2, 4.3** and **4.4**).

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

Patients with Impaired renal function:

The pharmacokinetics 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 of abiraterone acetate in patients with renal impairment, including severe renal impairment, does not require dose reduction (see section 4.2).

5.3 Preclinical safety data

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

reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

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

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

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

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

Environmental Risk Assessment (ERA):

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Colloidal silicon dioxide
- Croscarmellose sodium
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose
- Povidone
- Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in the original container at or below 25 °C.

Protect from light

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

Pregnant women or those who may be pregnant must use protection such as gloves when handling (touching) ABIRATERONE CIPLA (see **sections 4.3 and 4.2**).

6.5 Nature and contents of container

ABIRATERONE CIPLA is marketed in pack sizes of 120 tablets per pack, in white, opaque, round HDPE bottles fitted with white PP child resistant closures with a liner.

6.6 Special precautions for disposal and other handling:

Based on its mechanism of action, ABIRATERONE CIPLA may harm a developing foetus; Therefore, women who are pregnant or may be pregnant including healthcare workers should not handle ABIRATERONE CIPLA without protection, such as gloves (see **section 4.6**).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

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Mispel Street,

Belville, 7530,

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Company Contact Details:

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Customer Care: 080 222 6662

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8. REGISTRATION NUMBER

52/21.12/0144

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 June 2020

10. DATE OF REVISION OF THE TEXT

Not applicable