SCHEDULING STATUS:

PROPRIETARY NAME (and dosage form):

Atacand PLUS 16/12,5 mg (Tablet)

Atacand PLUS 32/12,5 mg (Tablet)

Atacand PLUS 32/25 mg (Tablet)

COMPOSITION:

One ATACAND PLUS 16/12,5 mg tablet contains 16 mg candesartan cilexetil and 12,5 mg hydrochlorothiazide.

One ATACAND PLUS 32/12,5 mg tablet contains 32 mg candesartan cilexetil and 12,5 mg hydrochlorothiazide.

One ATACAND PLUS 32/25 mg tablet contains 32 mg candesartan cilexetil and 25 mg hydrochlorothiazide.

List of excipients: calcium carboxymethylcellulose, hydroxypropylcellulose, iron oxide, lactose monohydrate, magnesium stearate, maize starch, polyethylene glycol.

Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Candesartan cilexetil:

Candesartan cilexetil is a prodrug. After oral administration it is converted to the active medicine, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT_1 receptors, with tight binding to and slow dissociation

from the receptor. It has no agonist activity.

The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type I (AT_1) receptor.

The antagonism of the AT_1 receptors results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide:

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules, and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid and
reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

Candesartan cilexetil and hydrochlorothiazide:

Candesartan and hydrochlorothiazide have additive antihypertensive effects.

In hypertensive patients, ATACAND PLUS results in a dose-dependent and sustained reduction in arterial blood pressure without reflex increase in heart rate. There is no indication of serious or exaggerated first-dose hypotension or rebound effect after cessation of treatment. After administration of a single dose of ATACAND PLUS, onset of the antihypertensive effect generally begins within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within 4 weeks and is sustained during long-term treatment.

Pharmacokinetic properties:

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product.

Absorption and distribution:

Candesartan cilexetil:

Following oral administration, candesartan cilexetil is converted to the active medicine candesartan. The mean peak serum concentration (C_{max}) is reached 3-4 hours following tablet intake. No gender-related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 99 %). The apparent volume of distribution of candesartan is 0,1 litres/kg.

Hydrochlorothiazide:

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70 %. Concomitant intake of food increases the absorption by approximately 15 %. The bioavailability may decrease in patients with cardiac failure and pronounced oedema.

The plasma protein binding of hydrochlorothiazide is approximately 60 %. The apparent volume of distribution is approximately 0,8 litres/kg.

Metabolism and elimination:

Candesartan cilexetil:

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4.

Based on *in vitro* data, no interaction would be expected to occur *in vivo* with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal

half-life (t½) of candesartan is approximately 9 hours. There is no accumulation following multiple doses. The half-life of candesartan remains unchanged (approximately 9 hours) after

administration of candesartan cilexetil in combination with hydrochlorothiazide. No accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

Total plasma clearance of candesartan is about 0,37 ml/min/kg, with a renal clearance of about 0,19 ml/min/kg. Following an oral dose of ^{14}C-labelled candesartan cilexetil, the active candesartan, and its inactive metabolites are excreted via the urine (30 %) and to a larger extent (70 %) via the faeces.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged compound by glomerular filtration and active tubular secretion. The terminal $t_{½}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70 % of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (approximately 8 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Pharmacokinetics in special populations:

Candesartan cilexetil:

In elderly subjects (over 65 years), C_{max} and AUC of candesartan are increased by approximately 50 % and 80 %, respectively in comparison to young adults.

In patients with mild (Ccr 60-90 ml/min) and moderate (Ccr 30-60 ml/min) to severe (Ccr 15-30 ml/min) renal impairment, C_{max} and AUC of candesartan increased during repeated dosing.

In patients with mild to moderate renal impairment AUC was approximately doubled, while in severe renal

impairment the AUC was further increased. The terminal $t_{½}$ of candesartan in patients with severe renal impairment was approximately doubled compared to patients with normal renal function. Candesartan has not been studied in patients with more severe renal failure (Ccr ≤ 15 ml/min).

Candesartan is not eliminated by haemodialysis in severe renal impairment.

In patients with mild hepatic impairment, there was an increase in the AUC of candesartan, of approximately 30 %. In patients with moderate hepatic impairment, the increase in the AUC of candesartan was approximately 145 %.

Hydrochlorothiazide:

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

INDICATIONS:

ATACAND PLUS is indicated for essential hypertension in patients stabilised on the individual components given at the same dosages.

CONTRAINDICATIONS:

- Moderate to severe hepatic impairment and/or cholestasis
- Gout
- Sensitivity to any of the components of ATACAND PLUS
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Moderate to severe renal function impairment (creatinine clearance < 30 ml/min)
- Bilateral renal artery stenosis

- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
- Porphyria
- ATACAND PLUS contains a thiazide diuretic in (fixed dose) and therefore should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines
- Lithium therapy: Concomitant administration with ATACAND PLUS may lead to toxic blood concentrations of lithium (see "INTERACTIONS")
- Pregnancy and lactation (see "PREGNANCY AND LACTATION")

WARNINGS:

When ATACAND PLUS is used in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end-stage renal impairment (creatinine clearance ≤ 15 ml/min/1,73 m^2 BSA).

Prolongation of INR and bleeding complications with concomitant warfarin therapy may occur.

Lithium toxicity may occur when ATACAND PLUS is used in combination with lithium therapy (see "INTERACTIONS").

Refer to "PREGNANCY AND LACTATION" for warnings.

INTERACTIONS:

No drug interactions of clinical significance have been identified for candesartan cilexetil. Compounds which have formally been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide and nifedipine.

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Post marketing report suggests a rare but significant interaction with prolongation of INR and bleeding, with concomitant warfarin therapy.

The bioavailability of candesartan is not affected by food.

The antihypertensive effect of ATACAND PLUS may be enhanced by other antihypertensives.

The potassium-depleting effect of hydrochlorothiazide could be expected to be potentiated by other medicines associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivatives).

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and anti-arrhythmics. Periodic monitoring of serum potassium is recommended when ATACAND PLUS is administered with such medicines.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ATACAND PLUS. Careful monitoring of serum lithium levels is recommended during concomitant use.

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect on non-depolarizing skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or

Vitamin D must be prescribed, serum calcium levels should be monitored and dosage adjusted accordingly.

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide- type diuretics by decreasing gastrointestinal motility and stomach-emptying rate.
Thiazides may increase the risk of adverse effects caused by amantadine.

Thiazides may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.
Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Hydrochlorothiazide may cause the arterial response to pressor amines (e.g. adrenaline) to decrease but not enough to exclude a pressor effect.

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with high doses of iodinated contrast media.

There is no clinically significant interaction between hydrochlorothiazide and food.

PREGNANCY AND LACTATION:

Use in pregnancy:

Should a woman become pregnant while receiving ATACAND PLUS, the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication.

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. These medicines pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration in the second and third trimester. Cases of defective skull ossification have been observed. Premature and low birth mass can occur.

ATACAND PLUS is contraindicated in pregnancy (see "CONTRAINDICATIONS").

Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.

Lactation:

Candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breast-feeding should be discontinued if the use of ATACAND PLUS is considered essential (see "CONTRAINDICATIONS").

DOSAGE AND DIRECTIONS FOR USE:

ATACAND PLUS should be taken once daily and may be taken with or without food.

Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Use in the elderly:

No special dosage recommendations.

Use in impaired renal function:

ATACAND PLUS should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 60 ml/min/1,73 m^2 BSA).

Use in impaired hepatic function:

ATACAND PLUS should not be used in patients with moderate to severe hepatic impairment and/or cholestasis.

Use in children:

The safety and efficacy of ATACAND PLUS have not been established in children.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The overall incidence of adverse events showed no association with age or gender.

Clinical adverse events, regardless of causal relationship, with a cumulative 8-week incidence rate of ≥ 1 % during treatment with candesartan cilexetil/hydrochlorothiazide up to 16/12,5 mg in double-blind placebo controlled trials are presented in the following table:

	Placebo (n = 526) %	Candesartan cilexetil/ hydrochlorothiazide (n = 1 025) %
Cardiovascular: Tachycardia	0,8	1,1
Gastrointestinal: Abdominal pain	0,8	1,0

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Nausea	0,6	1,3
Musculo-skeletal: Back pain	 2,4	 3,0
Nervous System: Headache Dizziness	 5,5 1,2	 3,2 2,6
Respiratory: Respiratory infection Bronchitis Pharyngitis Sinusitis	 1,4 1,4 1,0 1,6	 2,5 1,7 1,0 1,7
Other:		
Influenza-like symptoms	1,6	2,1
Urinary tract infection	0,4	1,4
Inflicted injury	1,2	1,2
Fatigue	0,8	1,1

Clinical adverse events, regardless of causal relationship, occurring in ≥ 1 % of the patients during 8-week randomised treatment with candesartan cilexetil/hydrochlorothiazide 32/12,5 mg and 32/25 mg in double-blind clinical trials are presented in the following table:

	Placebo (n = 163) %	Candesartan cilexetil/ hydrochlorothiazide (n = 1 873) %
Metabolism and nutrition disorders: Dyslipidaemia	 0	 2,8
Nervous system disorders: Dizziness	 0,6	 2,8

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Headache	7,4	2,1
Musculoskeletal and connective tissue disorder: Back pain	 2,5	 1,9
Infections and infestations: Nasopharyngitis Bronchitis	 0 1,2	 1,4 1,0
Respiratory, thoracic and mediastinal disorders: Cough	 1,2	 1,0
General disorders and administration site conditions: Fatigue	 2,5	 1,0

Candesartan cilexetil:

The following adverse reactions have been reported very rarely (≤ 1/10 000) with candesartan cilexetil in post-marketing experience:

Very rare: ≤ 1/10 000	*Blood and lymphatic system disorders:*	Leukopenia, neutropenia and agranulocytosis
	Metabolism and nutrition disorders:	Hyperkalaemia, hyponatraemia
	Hepato-biliary disorders:	Increased liver enzymes, abnormal hepatic function or hepatitis
	Skin and subcutaneous tissue disorders:	Angioedema, rash, urticaria, pruritis

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	Musculoskeletal, connective tissue and bone disorders	Back pain
	Renal and urinary disorders:	Renal impairment, including renal failure in susceptible patients

Hydrochlorothiazide

The following adverse reactions have been reported with hydrochlorothiazide monotherapy, usually in doses of 25 mg or greater. The frequencies used are: Common (≥ 1/100), Uncommon (≥ 1/1 000 and ≤ 1/100) and Rare (≤ 1/1 000).

Common (≥ 1/100)	*Metabolism and nutrition disorders:*	Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia)
	Nervous system disorders:	Light-headedness, vertigo
	Renal and urinary disorders:	Glycosuria
	General disorders and administration site conditions:	Weakness
	Investigations:	Increases in cholesterol and triglycerides
Uncommon (≥ 1/1 000 and ≤ 1/100)	*Vascular disorders:*	Postural hypotension
	Gastrointestinal disorders:	Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation
	Skin and subcutaneous tissue disorders:	Rash, urticaria, photosensitivity reactions
Rare (≤ 1/1 000)	*Blood and lymphatic system disorders:*	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
	Immune system disorders:	Anaphylactic reactions
	Psychiatric disorders:	Sleep disturbances, depression, restlessness

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	Nervous system disorders:	Paraesthesia
	Eye disorders:	Transient blurred vision
	Cardiac disorders:	Cardiac arrhythmias
	Vascular disorders:	Necrotising angitis (vasculitis, cutaneous vasculitis)
	Respiratory, thoracic and mediastinal disorders:	Respiratory distress (including pneumonitis and pulmonary oedema)
	Gastrointestinal disorders:	Pancreatitis
	Hepato-biliary disorders:	Jaundice (intrahepatic cholestatic jaundice)
	Skin and subcutaneous tissue disorders:	Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
	Musculoskeletal and connective tissue disorders:	Muscle spasm
	Renal and urinary disorders:	Renal dysfunction and interstitial nephritis
	General disorders and administration site conditions:	Fever
	Investigations:	Increases in urea and serum creatinine

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Laboratory findings:

Increases in serum uric acid, serum creatinine, serum urea, serum potassium, blood glucose and serum alanine transaminase (ALT) may occur. Decreases in haemoglobin and increases in serum aspartate transaminase

(AST) have been observed in patients receiving ATACAND PLUS.

Special precautions:

Renal artery stenosis:

ATACAND PLUS may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Anaesthesia and surgery:

Hypotension may occur during anaesthesia and surgery in patients treated with ATACAND PLUS due to blockade of the renin-angiotensin-aldosterone system. This may be severe such that additional intravenous fluids and/or vasopressors are needed.

Intravascular volume depletion:

In patients with intravascular volume and/or sodium depletion, symptomatic hypotension may occur. Therefore, the use of ATACAND PLUS is not recommended until this condition has been corrected.

Renal impairment/kidney transplantation:

When ATACAND PLUS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid levels is recommended. Loop diuretics are preferred to ATACAND PLUS in this population.

There is no experience regarding the administration of ATACAND PLUS in patients with recent kidney transplantation.

Hepatic impairment:

There is no experience in patients with moderate to severe hepatic impairment and/or cholestasis.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy:

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy (see "CONTRAINDICATIONS").

Electrolyte imbalance:

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

ATACAND PLUS can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis).

Marked hypercalcaemia may be a sign of hyperparathyroidism. ATACAND PLUS should be discontinued before carrying out tests for parathyroid function.

Hydrochlorothiazide (a component of ATACAND PLUS) dose-dependently increases urinary potassium excretion which may result in hypokalaemia, e.g. in liver cirrhosis, after brisk diuresis, inadequate intake of electrolytes and in patients receiving corticosteroids. Concomitant use of ATACAND PLUS and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicines that may increase potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.

Metabolic and endocrine effects:

Treatment with ATACAND PLUS may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required. Latent diabetes mellitus may manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with hydrochlorothiazide therapy. At the doses contained in ATACAND PLUS only minimal effects were observed. Hydrochlorothiazide may increase serum uric acid concentration and may precipitate gout in susceptible patients.

General:

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease,

including renal artery stenosis), treatment with medicines that affect this system such as ATACAND PLUS has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure as has been observed in post marketing data. Excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease may result in a myocardial infarction or stroke.

Effects on ability to drive and use machines:

The effect of ATACAND PLUS on the ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In single case reports of overdose (up to 672 mg candesartan cilexetil) patient recovery was uneventful.

The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

Management:

No specific information is available on the treatment of overdosage with ATACAND PLUS. The following measures are, however, suggested in case of overdosage.

When indicated, induction of vomiting or gastric lavage should be considered. If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored.

Candesartan is not removed by haemodialysis. It is not known to what extent hydrochlorothiazide is removed

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by haemodialysis.

IDENTIFICATION:

ATACAND PLUS 16/12,5 mg tablets are peach, oval, biconvex tablets with a score on both sides and engraved *A/CS.*

ATACAND PLUS 32/12,5 mg tablets are yellow, oval, biconvex tablets with a score and engraving *A/CJ* on one side and a pressure sensitive bisect on the reverse side.

ATACAND PLUS 32/25 mg tablets are pink, oval, biconvex tablets with a score and engraving *A/CD* on one side and a pressure sensitive bisect on the reverse side.

The tablets can be divided into equal halves.

PRESENTATION:

ATACAND PLUS 16/12,5 mg; 32/12,5 mg; 32/25 mg:

Available in clear PVC/PVDC/aluminium blister packs of 28 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not remove blister from carton until required for use.

Keep out of reach of children.

REGISTRATION NUMBERS:

ATACAND PLUS 16/12,5 mg:	35/7.1.3/0098
ATACAND PLUS 32/12,5 mg:	43/7.1.3/0922
ATACAND PLUS 32/25 mg:	43/7.1.3/0923

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Equity Pharmaceuticals (Pty) Ltd.

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100 Sovereign Drive, Route 21

Corporate Park, Nellmapius Drive,

Irene, Pretoria, South Africa

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