FINAL PACKAGE INSERT

SCHEDULING STATUS: **S3**

PROPRIETARY NAME (and dosage form):

Atacand® 8 mg, Atacand® 16 mg, Atacand® 32 mg (Tablet)

COMPOSITION:

Each ATACAND 8 mg tablet contains 8 mg candesartan cilexetil.

Each ATACAND 16 mg tablet contains 16 mg candesartan cilexetil.

Each ATACAND 32 mg tablet contains 32 mg candesartan cilexetil.

Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Candesartan cilexetil is a prodrug. After oral administration it is converted to the active drug, 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 1 (AT_1) receptor.

The antagonism of the angiotensin II (AT_1) receptors results in dose related increases in plasma renin activity, angiotensin I and angiotensin II concentrations, and a decrease in plasma aldosterone concentration.

Hypertension:

In hypertension ATACAND causes a dose-related sustained reduction in arterial blood pressure over the dosage interval. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected.

After administration of a single dose of ATACAND, onset of antihypertensive effect generally begins within 2 hours. With continuous treatment, the maximum reduction in blood pressure is generally attained within 4 weeks and is sustained during long-term treatment. Candesartan has a peak to trough ratio of peak versus trough effects of close to 1.

ATACAND increases renal blood flow and either has no effect on, or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced.

ATACAND also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension and microalbuminuria.

Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

Heart Failure:

In patients with chronic heart failure (CHF) and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF ≤ 40%), ATACAND decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

Treatment with ATACAND reduces mortality due to cardiovascular events and hospitalisation due to CHF in patients with a left ventricular ejection fraction (LVEF) of ≤ 40% and improves symptoms in these patients as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) programme.

There was no benefit of ATACAND in patients with a LVEF of more than 40%.

Pharmacokinetic properties:

Absorption and distribution:

Following oral administration, candesartan cilexetil is converted to the active drug, candesartan.

The mean peak serum concentration (C_{max}) is reached 3 to 4 hours following tablet intake.

The candesartan serum concentration increases linearly with increasing doses in the therapeutic dose range.

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.

Metabolism and elimination:

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 drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

The total plasma clearance of candesartan is about 0,37 ml/min/kg, with 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 metabolite are excreted via the urine (30%) and to a larger extent (70%) via the faeces.

Pharmacokinetics in special populations:

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

In patients with mild (creatinine clearance 60-90 ml/min) and moderate (creatinine clearance 30-60 ml/min) to severe (creatinine clearance 15-30 ml/min) renal impairment, C_{max} and AUC of candesartan increased during repeated dosing. The $t_{1/2}$ and AUC 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 (creatinine clearance < 15ml/min).

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

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

INDICATIONS:

ATACAND is indicated for mild to moderate hypertension.

ATACAND can be used as monotherapy or in combination with other antihypertensive agents such as thiazide diuretics and dihydropyridine calcium antagonists, for enhanced efficacy.

Heart failure:

Treatment with ATACAND reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction (LVEF ≤ 40%).

CONTRA-INDICATIONS:

Hypersensitivity to any component of ATACAND.

Very severely impaired renal function (creatinine clearance < 15 ml/min) (see "*Warning*s").

Pregnancy and lactation (see *"Pregnancy and Lactation"*).

Severely impaired hepatic function.

Bilateral renal artery stenosis or stenosis in the presence of a single kidney.

Aortic valve stenosis or Hypertrophic Obstructive Cardiomyopathy (HOCM).

Angioedema on previous exposure to ATACAND or angiotensin receptor blockers (ARB's) or ACE inhibitors.

WARNINGS:

When ATACAND 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).

Refer to *"Pregnancy and Lactation"* section for warnings.

INTERACTIONS:

No interactions of clinical significance have been identified. Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with

ATACAND and careful monitoring of serum lithium levels is recommended during concomitant use.

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

The bioavailability of candesartan is not affected by food.

PREGNANCY AND LACTATION:

Use in pregnancy:

Should a woman become pregnant while receiving ATACAND, 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 is contra-indicated in pregnancy (see *"Contra-indications"*).

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 is considered essential (see *"Contra-indications"*).

DOSAGE AND DIRECTIONS FOR USE:

Dosage in hypertension:

The recommended initial dose of ATACAND is 8 mg once daily. The usual maintenance dose is 8 mg to 16 mg once daily.

The maximal antihypertensive effect is attained within 4 weeks of initiation of treatment.

Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

Use in elderly:

No initial dosage adjustment is necessary for elderly patients with normal renal and hepatic function.

Use in impaired renal function:

No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1,73m^2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 15-30 ml/min/1,73m^2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used.

Use in impaired hepatic function:

No initial dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no experience available in patients with severe hepatic impairment and/or cholestasis (see *"Contra-indications"*).

Concomitant therapy:

ATACAND can be used as monotherapy or in combination with other antihypertensive agents, such as thiazide diuretics and dihydropyridine calcium antagonists, e.g. amlodipine, for enhanced efficacy.

Use in black patients:

The antihypertensive effect of ATACAND is less in black than non-black (Caucasian, Asian and other) patients. Consequently, uptitration of ATACAND and concomitant therapy (such as thiazide diuretics) may be more frequently needed for blood pressure control in black than non-black patients.

Dosage in heart failure:

The usual recommended initial dose of ATACAND is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see *"Special precautions"*).

Special patient populations:

No initial dose adjustment is necessary for elderly patients or in patients with renal or mild to moderate hepatic impairment.

Concomitant therapy:

ATACAND can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products (see *"Pharmacodynamic properties"*).

Administration:

ATACAND should be taken once daily with or without food.

Use in children:

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Treatment of hypertension:

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

In a pooled analysis of clinical trial data, the following common (> 1/100) adverse reactions with candesartan cilexetil were reported based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo.

Infections and infestations:

Common: Respiratory infection.

Nervous system disorders:

Common: Dizziness/vertigo, headache.

Laboratory findings:

Small decreases in haemoglobin have been seen. Significant increases in creatinine, urea or potassium and decrease in sodium have been observed. In patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

Treatment of heart failure:

The adverse experience profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical programme, comparing ATACAND in doses up to 32 mg (n = 3,803) to placebo (n = 3,796), 21,0% of the candesartan cilexetil group and 16,1% of the placebo group discontinued treatment because of adverse events.

Adverse reactions commonly (≥ 1/100, < 1/10) seen were:

Vascular disorders: Hypotension

Metabolism and nutrition disorders: Hyperkalaemia

Renal and urinary disorders: Renal impairment

Laboratory findings:

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see "*Special precautions*").

Post marketing:

The following adverse reactions have been reported very rarely (< 1/10,000) in post marketing experience:

Blood and lymphatic system disorders: Leucopenia, 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: Angio-oedema, rash, urticaria, pruritus

Musculoskeletal, connective tissue and bone disorders: Back pain

Renal and urinary disorders: Renal impairment, including renal failure in susceptible patients (see "*Special precautions*")

Special precautions:

Hypotension:

Hypotension may occur during treatment with ATACAND in heart failure patients. As described for other agents acting on the renin-angiotensin-aldosterone system, it may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted.

Renal artery stenosis:

Medicines that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal impairment:

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with ATACAND.

When ATACAND is used in hypertensive 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 (i.e. creatinine clearance < 15 ml/min/1,73 m^2 BSA).

Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of ATACAND, monitoring of serum creatinine and potassium is recommended.

Kidney transplantation:

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

Hepatic impairment:

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

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy):

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy (see *"Contra-indications"*).

Hyperkalaemia:

Concomitant use of ATACAND with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that may increase potassium levels (e.g. spironolactone and heparin) may lead to increases in serum potassium in hypertensive patients.

In heart failure patients treated with ATACAND, hyperkalaemia may occur. During treatment with ATACAND in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

Anaesthesia and surgery:

Hypotension may occur during anaesthesia and surgery in patients treated with ATACAND due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. Excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Effects on ability to drive and use machines:

The effect of ATACAND 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 dizziness or weariness may occur during treatment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness.

In single case reports of overdose (up to 672 mg candesartan cilexetil) patient recovery was uneventful.

Management:

If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored.

Candesartan is not removed by haemodialysis.

IDENTIFICATION:

ATACAND 8 mg:

A light pink, circular, biconvex tablet with a score and engraved A/CG on one side and 008 on the other side.

ATACAND 16 mg:

A pink, circular, biconvex tablet with a score and engraved A/CH on one side and 016 on the other side.

ATACAND 32 mg:

A pink, circular, biconvex tablet with a score and engraved A/CL on one side and 032 on the other side.

PRESENTATION:

ATACAND 8 and 16 mg:

PVC/PVDC blister packs of 7, 14, 28, 56 or 98 tablets in strips of 7 or 30 tablets in blister strips of 10 or 15.

White HDPE bottles of 30 or 100 tablets.

ATACAND 32 mg:

PVC/PVDC blister packs of 7, 14, 28, 56 or 98 tablets in strips of 7 or 30 tablets in blister strips of 10 or 15.

White HDPE bottles of 100 tablets.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep out of reach of children.

REGISTRATION NUMBERS:

ATACAND 8 mg: 32/7.1.3/0099

ATACAND 16 mg: 32/7.1.3/0100

ATACAND 32 mg: A39/7.1.3/0244

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

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

8 February 2008

Manufactured under licence from Takeda Pharmaceuticals Company Limited.

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CDS: 8 July 2005

Inclusion of Namibia + Botswana registration details (15-10-2010)

Atacand 8 mg NAMIBIA: NS2 Reg. No.: 06/7.1.3/0309	Atacand 16 mg NAMIBIA: NS2 Reg. No.: 04/7.1.3/1818	Atacand 32 mg NAMIBIA: NS2 Reg. No.: 12/7.1.3/0078

Atacand 8 mg BOTSWANA: S2 Reg. No.: BOT 1101812	Atacand 16 mg BOTSWANA: S2 Reg. No.: BOT 0700945