SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIVAZAC® PLUS 150

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Irbesatan 150 mg

Excipients with known effects
Each tablet contains 55.5 mg of Lactose as a monohydrate

3. PHARMACEUTICAL FORM

Tablet,
White biconvex caplet shape tablet embossed with E41 on one side and plane on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of essential hypertension.
VIVAZAC® is indicated in adults for the treatment of essential hypertension. It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen

4.2 Posology and method of administration

Route of administration: Orally.
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in hemodialyzed patients and in the elderly over 75 years. In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other antihypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan. In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure. Special Populations Renal impairment: no dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis. Hepatic impairment: no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment. Older people: although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for older people. Paediatric population: the safety and efficacy of Irbesartan in children aged 0 to 18 has not been established. no recommendation on a posology can be made.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimesters of pregnancy.

- The concomitant use of Irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR)

4.4 Special warnings and precautions for use

As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Paediatric population: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Irbesartan
Aliskiren-containing products or ACE-inhibitors: dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent
Potassium supplements and potassium-sparing diuretics: based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, and salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended
Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Additional information on irbesartan interactions: The pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolized by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin, a medicinal product metabolized by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was

not altered by coadministration of irbesartan.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Angiotensin II Receptor Antagonists (AIIRAs):

The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Breast-feeding: Because no information is available regarding the use of Irbesartan during breast-feeding, Irbesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant. It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk

Fertility Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment. Undesirable effects

4.8 Undesirable effects

In patients with hypertension, the overall incidence of adverse events did not differ. Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients. The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, race, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in patients (i.e., uncommon)

The following table presents the adverse drug reactions. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions additionally reported from post–marketing experience are also listed. These adverse reactions are derived from spontaneous reports

Immune system disorders:

Not known: hypersensitivity reactions such as angioedema, rash, urticaria

Metabolism and nutrition disorders:

Not known: hyperkalaemia

Nervous system disorders:

Common: dizziness, orthostatic dizziness* Not known: vertigo, headache Ear and labyrinth disorder: Not known: tinnitus

Cardiac disorders:

Uncommon: tachycardia

Vascular disorders:

Common: orthostatic hypotension*

Uncommon: flushing

Respiratory, thoracic and mediastinal disorders:

Uncommon: cough

Gastrointestinal disorders:

Common: nausea/vomiting

Uncommon: diarrhoea, dyspepsia/heartburn

Not known: dysgeusia

Hepatobiliary disorders:

Uncommon: jaundice

Not known: hepatitis, abnormal liver function

Skin and subcutaneous tissue disorders:

Not known: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders:

Common: musculoskeletal pain*

Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps Renal and urinary disorders:

Not known: impaired renal function including cases of renal failure in patients at risk

Reproductive system and breast disorders:

Uncommon: sexual dysfunction

General disorders and administration site conditions:

Common: fatigue

Uncommon: chest pain

Investigations:

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia occurred in patients in the irbesartan 300 mg group. In diabetic hypertensive patients with chronic renal insufficiency and overt

proteinuria, hyperkalaemia occurred in patients in the irbesartan group.

Common: Significant increases in plasma creatine kinase were commonly observed in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric population:

In hypertensive children and adolescents aged 6 to 16 years, the following adverse reactions occurred inheadache, hypotensiondizziness, cough. In the the most frequent laboratory abnormalities observed were creatinine increases and elevated CK values in child recipients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health providers are asked to report any suspected adverse reactions to marketing authorization holder, or if available, via the national reporting system (see details below)

- *Paper based reporting: TMDA yellow card*
- *Online reporting: https://sqrt.tmda.go.tz/*
- *USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Angiotensin-II antagonists, plain. ATC code: C09C A04.
Mechanism of action: Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

Clinical efficacy:

Hypertension

Irbesartan lowers blood pressure with minimal change in heart rate. The decrease in blood pressure is dose-related for once a day doses with a tendency towards plateau at doses above 300 mg. Doses of 150-300 mg once daily lower supine or seated blood pressures at trough (i.e. 24 hours after dosing) by an average of 8-13/5-8 mm Hg (systolic/diastolic).

Peak reduction of blood pressure is achieved within 3-6 hours after administration and the blood pressure lowering effect is maintained for at least 24 hours. At 24 hours the reduction of blood pressure was 60-70% of the corresponding peak diastolic and systolic responses at the recommended doses. Once daily dosing with 150 mg produced trough and mean 24 hour responses similar to twice daily dosing on the same total dose.

The blood pressure lowering effect of Irbesartan is evident within 1-2 weeks, with the maximal effect occurring by 4-6 weeks after start of therapy. The antihypertensive effects are maintained during long term therapy. After withdrawal of therapy, blood pressure gradually returns toward baseline. Rebound hypertension has not been observed.

The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive.

The efficacy of Irbesartan is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.

There is no clinically important effect on serum uric acid or urinary uric acid secretion.

Paediatric population

Reduction of blood pressure with 0.5 mg/kg (low), 1.5 mg/kg (medium) and 4.5 mg/kg (high) target titrated doses of irbesartan was evaluated in hypertensive or at risk (diabetic, family history of hypertension) children and adolescents aged 6 to 16 years over a three week period. No significant difference was apparent between these doses. Adjusted mean change of trough seated diastolic blood pressure (SeDBP) was as follows: 3.8 mmHg (low dose), 3.2 mmHg (medium dose), 5.6 mmHg (high dose).

Hypertension and type 2 diabetes with renal disease

The “Irbesartan Diabetic Nephropathyirbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria.When the individual components of the primary endpoint were analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

Subgroups consisting of gender, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black subgroups which representeda renal benefit was not evident, although the confidence intervals do not exclude it. As for the secondary endpoint of fatal and non-fatal cardiovascular events, there was no difference among the three groups in the overall population, although an increased incidence of non-fatal MI was seen for women and a decreased incidence of non-fatal MI was seen in males in the irbesartan group versus the based regimen. An increased incidence of non-fatal MI and stroke was seen in females in the irbesartan-based regimen versus the amlodipine-based regimen, while hospitalization due to heart failure was reduced in the overall population. However, no proper explanation for these findings in women has been identified.

Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus: irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. Examined the long-term effects (2 years) of Irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate (UAER) > 300 mg/day, and an increase in UAER of at least 30% from baseline). The predefined blood pressure goal was ≤ 135/85 mmHg. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve the blood pressure goal. While similar blood pressure was achieved in all treatment groups, fewer subjects reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction for the higher dose. An accompanying improvement in the glomerular filtration rate (GFR) was not observed during the first three months of treatment. The slowing in the progression to

clinical proteinuria was evident as early as three months and continued over the 2 year period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan 300 mg group.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

No significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

Aliskiren in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints: Cardiovascular death and stroke were both numerically more frequent in the aliskiren group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group.

5.2 Pharmacokinetic properties

After oral administration, irbesartan is well absorbed: absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 litres. Following oral or intravenous administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%).

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in older subjects (≥ 65 years) than those of young subjects (18 - 40 years). However, the terminal half-life was not significantly altered. No dosage adjustment is necessary in older people.

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of 14C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

Paediatric population

The pharmacokinetics of irbesartan were evaluated Results showed that Cmax, AUC and clearance rates were comparable to those observed in adult patients receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was observed upon repeated once daily dosing.

Renal impairment: in patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.
There was no evidence of mutagenicity, clastogenicity or carcinogenicity.
Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring. Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.
Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Croscarmellose sodium,
Pregelatinized Starch,
Hydroxypropyl methylcellulose,
Microcrystalline Cellulose,
Colloidal silicon dioxide,
Magnesium Stearate,
Opadry White O-YL 28900,

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

VIVAZAC® PLUS 300/25 F.C. Tablets: are packed in blisters (Aluminum foil & PVC coated PVDC) then packed in cardboard cartons with a multi-folded leaflet. Pack size: 30 F/C Tablets; (10 F/C Tablets /blister, 3 blisters/ pack).

6.6 Special precautions for disposal

Any unused product or waste should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MAH HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

TAN 20 HM 0405

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2020

10. DATE OF REVISION OF THE TEXT

Not available (New application)