SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:
Arbitense Tablets 50 mg

2. Qualitative & Quantitative Composition:
Each film-coated tablet contains 50 mg Losartan Potassium USP.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:
Film-coated Tablet
White to off white colored, oval shaped film coated tablets having '50' debossed on one side and 'n' on the other side.

4. Clinical Particulars:
4.1. ***Therapeutic indications:***

Losartan tablets are used in the treatment of:
- Hypertension in adults and in children and adolescents 6-18 years of age.
- Renal disease in adult patients with hypertension and type 2 diabetes mellitus withproteinuria ≥0.5 g/day as part of an antihypertensive treatment.
- Chronic heart failure in adult patients when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication.
- To reduce the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

4.2. ***Posology and method of administration:***
Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).
Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g.hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day. The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart failure
Patients with heart failure who have been stabilized with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
The usual initial dose of losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the

patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added, and/ or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

***Special Populations*:**
Use in patients with intravascular volume depletion

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered.

Use in patients with renal impairment and hemodialysis patients

No initial dosage adjustment is necessary in patients with renal impairment and in hemodialysis patients.

Use in patients with hepatic impairment
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Paediatric population
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6- 18 years old for the treatment of hypertension. Limited pharmacokinetic data are available in hypertensive children above one month of age.

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. (In exceptional cases the dose can be increased to a maximum of 100 mg once daily). Dosage should be adjusted according to blood pressure response.
In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in pediatric patients.
Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m^2,as no data are available.
Losartan is also not recommended in children with hepatic impairment.

Use in elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration
Losartan tablets should be swallowed with a glass of water. Arbitense may be administered with or without food.

4.3. *Contraindications*:
Hypersensitivity to the active substance or to any of the excipients. 2nd and 3rd trimester of pregnancy.
Severe hepatic impairment.

4.4. *Special warning & precautions for use:*

Hypersensitivity

Angio-oedema. Patients with a history of angio-oedema (swelling of the face, lips, throat,and/ or tongue) should be closely monitored.

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan as compared to the placebo group. Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium- containing salt substitutes with losartan is not recommended.

Hepatic impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore, losartan must not be administered in patients with severe hepatic impairment. Losartan is not recommended in children with hepaticimpairment.

Renal impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin- angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre- existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin- aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosisof the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in pediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate < 30 ml/ min/ 1.73 m^2 as no data are available.

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation

There is no experience in patients with recent kidneytransplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.
There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Excipients
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 medicine.

Pregnancy
Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, losartan 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.

4.5. *Interaction with other medicinal products & other forms of interaction:*
Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.
Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active

carboxy- acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential,serum lithium level monitoring is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics 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.

Dual blockade (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function. Some studies have shown that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) as comparedto use of a single renin-angiotensin- aldosterone system agent.

4.6. *Pregnancy & lactation*

Pregnancy

The use of losartan is not recommended during the first trimester of pregnancy. The use oflosartan is contra-indicated during the 2nd and 3rd trimester 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, asmall increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan 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 losartan have occurred from

the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed forhypotension.

Breastfeeding
Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7. *Effects on ability to drive & use machines:*
No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8. *Undesirable effects:*
Losartan has been evaluated in clinical studies as follows:
- In a controlled clinical trial in >3,000 adult patients 18 years of age and older for essential hypertension
- In a controlled clinical trial in 177 hypertensive pediatric patients 6 to 16 years of age
- In a controlled clinical trial in >9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- In controlled clinical trials in >7,700 adult patients with chronic heart failure
- In a controlled clinical trial in >1,500 type 2 diabetic patients 31 years of age and older with proteinuria

In these clinical trials, the most common adverse event was dizziness.
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), not known (cannot be estimated from the available data).*

Hypertension

System organ class	**Adverse reaction**	**Frequency**
Nervous system disorders	dizziness, vertigo	Common
	somnolence, headache, sleep disorders	Uncommon
Cardiac disorders	palpitations, angina pectoris	Uncommon
Vascular disorders	symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose- related orthostatic effects, rash	Uncommon
Gastrointestinal disorders	abdominal pain, obstipation	Uncommon
General disorders and administration site conditions	asthenia, fatigue, oedema	Uncommon
	hyperkalemia	Common

Investigations	Increased alanine aminotransferase (ALT)*	Rare

*Usually resolved upon discontinuation

Hypertensive patients with left ventricular hypertrophy

In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy the following adverse events were reported:

System organ class	**Adverse reaction**	**Frequency**
Nervous system disorders	dizziness	common
Ear and labyrinth disorders	vertigo	common
General disorders and administration site conditions	asthenia/fatigue	common

Chronic heart failure

In controlled clinical trials in patients with chronic heart failure, the following adverse events were reported:

System organ class	**Adverse reaction**	**Frequency**
Nervous system disorders	dizziness	common
	headache	uncommon
	paraesthesia	rare
Cardiac disorders	syncope, atrial fibrillation, cerebrovascular accident	rare
Vascular disorders	hypotension, including orthostatic hypotension	common
Blood and lymphatic system disorders	anaemia	common
Respiratory, thoracic and mediastinal disorders	dyspnoea, cough	uncommon
Gastrointestinal disorders	diarrhoea, nausea, vomiting	uncommon
Skin and subcutaneous tissue disorders	urticaria, pruritus, rash	uncommon
General disorders and administration site conditions	asthenia/fatigue	uncommon
Investigations	increase in blood urea, serum creatinine and serum potassium	common
Metabolism and nutrition disorders	hyperkalaemia	uncommon*
Renal and urinary disorders	renal impairmentrenal failure	

* common in patients who received 150 mg losartan instead of 50 mg losartan

Hypertension and type 2 diabetes with renal disease

In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria the most common drug-related adverse events which were reported for losartanare as follows:

System organ class	Adverse reaction	Frequency
Nervous system disorders	dizziness	common
Vascular disorders	hypotension	common
General disorders and administration site conditions	asthenia/fatigue	common
Investigations	hypoglycaemia hyperkalaemia*	common

* In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan tablets developed hyperkalaemia >5.5 mmol/l and 3.4% ofpatients treated with placebo.

The following adverse reactions occurred more often in patients receiving losartan than placebo:

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	anaemia	not known
Cardiac disorders	syncope, palpitations	not known
Vascular disorders	orthostatic hypotension	not known
Gastrointestinal disorders	diarrhoea	not known
Musculoskeletal and connective tissue disorders	back pain	not known
Renal and urinary disorders	urinary tract infections	not known
General disorders and administration site conditions	flu-like symptoms	not known

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	anaemia, thrombocytopenia	not known
Ear and labyrinth disorders	tinnitus	not known
Immune system disorders	hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patient's angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura	rare
Nervous system disorders	migraine	not known
Respiratory, thoracic and mediastinal disorders	cough	not known
Gastrointestinal disorders	diarrhoea, pancreatitis	not known
General disorders and administration site conditions	malaise	not known
Hepatobiliary disorders	hepatitis	rare
	liver function abnormalities	not known
Skin and subcutaneous tissue disorders	urticaria, pruritus, rash, photosensitivity	not known
Muscoskeletal and connective tissue disorders	myalgia, arthralgia, rhabdomyolysis	not known
Reproductive system and breast disorders	erectile dysfunction/impotence	not known
Psychiatric disorders	depression	not known
Investigations	hyponatraemia	not known

Renal and urinary disorders
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy.

Pediatric population
The adverse reaction profile for pediatric patients appears to be similar to that seen in adultpatients. Data in the pediatric population are limited.

4.9. *Overdose*:
Symptoms of intoxication
Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment of intoxication
If symptomatic hypotension should occur, supportive treatment should be instituted. Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by hemodialysis.

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 medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the 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*.

5. Pharmacological Properties:
5.1. *Pharmacodynamics*:
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA01.

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevantactions of angiotensin II, regardless of the source or route of its synthesis.
Losartan does not have an agonist effect, nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit

ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II values fell within three days to the baseline values.
Both losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

5.2. *Pharmacokinetics:*

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartanand its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.
In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline poly exponentially, with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 50 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

Characteristics in patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolitedo not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as

in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women. In patients with mild to moderate alcohol-induced hepatic

cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers.
Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2- times higher in hemodialysis patients. The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor the active metabolite can be removed by hemodialysis.

Pharmacokinetics in pediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

5.3. *Preclinical Safety Data*:
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastro-intestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

6. Pharmaceutical Particulars:

6.1. *List of Excipients*:

S. No.	Material	Function
CORE TABLETS EXCIPIENTS		
1.	Microcrystalline Cellulose BP / Ph.Eur. (Grade 102)	Diluent
2.	Anhydrous Lactose BP (Pharmatose DCL 21)	Diluent
3.	Pregelatinised Starch BP (Starch 1500)	Disintegrant
4.	Magnesium Stearate Ph. Eur.	Lubricant
COATING EXCIPIENTS		
5.	Opadry White Y-1-7000	Coating mixture
6.	Purified Water	Coating solvent

6.2. Incompatibilities:
None known.

6.3. Proposed Shelf life:
36 months

6.4. Special precautions for storage:
Store below 30°C

6.5. Nature & contents of container:
Arbitense Tablets 50 mg are packed in blisters (using aluminum foil in both sides) placed in cartonalong with leaflet.
Alu/Alu blister of 3 x 10's

6.6. Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder and Manufacturing Site Addresses
Neopharma L.L.C
Plot A-1 89-95, Industrial City of Abu Dhabi (ICAD), Mussafah,
P.O. Box 72900, Abu Dhabi, **United Arab Emirates.**

8. Marketing Authorization Number
TAN 20 HM 0519

9. Date of First Registration
18/11/2020

10. Date of Revision of the Text