SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
VALVIX (TELMISARTAN AND AMLODIPINE TABLETS USP 40/5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besilate). Excipient(s) with known effect. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM : Film Coated Tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults:

Add on therapy

VALVIX 40/5 mg is indicated in adults whose blood pressure is not adequately controlled on amlodipine 5 mg alone.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of VALVIX containing the same component doses.

4.2 Posology and method of administration
Posology The recommended dose of this medicinal product is one tablet per day. The maximum recommended dose is one tablet 40 mg telmisartan/5 mg amlodipine per day. This medicinal product is indicated for long term treatment. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Add on therapy VALVIX 40 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg alone.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered Patients treated with 5 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to VALVIX 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of VALVIX containing the same component doses in one tablet once daily.

Elderly (> 65 years)

No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using telmisartan/amlodipine in such patients as amlodipine and telmisartan are not dialysable. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

VALVIX is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily.

Method of administration

Oral use.

VALVIX can be taken with or without food. It is recommended to take VALVIX with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction The concomitant use of telmisartan/amlodipine with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

4.4 Special warnings and precautions for use

Pregnancy Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Telmisartan/amlodipine should therefore be used with caution in these patients.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system (RAAS).

Renal impairment and kidney transplantation

When telmisartan/amlodipine is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

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 medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Patients with cardiac failure

In an amlodipine long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Elderly patients

The increase of the amlodipine dose should take place with care in the elderly patients.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions linked to the combination

No drug interaction studies have been performed.

<u>To be taken into account with concomitant use</u>

Other antihypertensive medicinal products

The blood pressure lowering effect of telmisartan/amlodipine can be increased by concomitant use of other antihypertensive medicinal products.

Medicinal products with blood pressure lowering potential

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Interactions linked to telmisartan

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other antihypertensive agents acting on the renin-angiotensin-aldosterone system (RAAS)

Clinical trial data has shown that 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.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Administration of VALVIX with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Telmisartan

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy . The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy .

Studies with telmisartan in animals have shown reproductive toxicity .

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, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist 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) (see section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension .

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses .

Breast-feeding Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Because no information is available regarding the use of telmisartan during breast-feeding, telmisartan/ amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility: No data from controlled clinical studies with the fixed dose combination or with the individual components are available. Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.

In preclinical studies, no effects of telmisartan on male and female fertility were observed. In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.7 Effects on ability to drive and use machines

VALVIX has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with VALVIX as well, even if not observed in clinical trials or during the post-marketing period.

Tabulated list of adverse reactions

The safety and tolerability of VALVIX has been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of whom received telmisartan in combination with amlodipine.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to

in each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Twynsta	Telmisartan	Amlodipine
Infections and infestations			
Uncommon		upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis	
Rare	cystitis	sepsis including fatal outcome[1]	
Blood and lymphatic system disorders:			
Uncommon		anaemia	

Rare		thrombocytopenia, eosinophilia	
Very rare			leukocytopenia, thrombocytopenia
Immune system disorders:			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
Metabolism and nutrition disorders			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in diabetic patients)	
Very rare			hyperglycaemia
Psychiatric disorders			
Uncommon			mood change
Rare	depression, anxiety, insomnia		confusion
Nervous system disorders			
Common	dizziness		
Uncommon	somnolence, migraine, headache, paraesthesia		
Rare	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor		
Very rare			extrapyramidal syndrome, hypertonia
Eye disorders			
Common			visual disturbance (including diplopia)
Uncommon			visual impairment

Rare		visual disturbance	
Ear and labyrinth disorders			
Uncommon	vertigo		tinnitus
	rash	outcome), drug eruption, toxic skin eruption, urticaria	
Very rare			angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			
Common			ankle swelling
Uncommon	arthralgia, muscle spasms (cramps in legs), myalgia		
Rare	back pain, pain in extremity (leg pain)	tendon pain (tendinitis like symptoms)	
Renal and urinary disorders			
Uncommon		renal impairment including acute renal failure	micturition disorder, pollakiuria
Rare	nocturia		
Reproductive system and breast disorders			
Uncommon	erectile dysfunction		gynaecomastia
General disorders and administration site condition			
Common	peripheral oedema		
Uncommon	asthenia, chest pain, fatigue, oedema		pain
Rare	malaise	influenza-like illness	
Investigations			

Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased
Rare	blood uric acid increased	blood creatine phosphokinase increased, haemoglobin decreased	

1: the event may be a chance finding or related to a mechanism currently not known

2: most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

3: cases of interstitial lung disease (predominantly interstitial pneumonia and eosinophilic pneumonia) have been reported from post-marketing experience with telmisartan

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. Themost prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia;bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflextachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

The patient should be closely monitored, and the treatment should be symptomatic and supportive.Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both telmisartan and amlodipine. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacementgiven quickly. Supportive treatment should be instituted.Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 5 mg has been shown to reduce the absorption rate of amlodipine. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers, ATC code: C09DB04. Twynsta

combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Twynsta once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting.

Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, an 40 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due

to the slow onset of action, acute hypotension is not a feature of amlodipine administration. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Twynsta in all subsets of the paediatric population in hypertension.

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination

The rate and extent of absorption of Twynsta are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 l.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination halflife of >20 hours. The maximum plasma concentration (Cmax) and, to a smaller

extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

Amlodipine exhibits linear pharmacokinetics.

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Gender

Differences in plasma concentrations of telmisartan were observed, with Cmax and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ in young and elderly patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/5 mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance. No clear

evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offspring such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at doses approximately 50 times greater than the maximum recommended dose for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 5 mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 5 mg/day on an mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide
Purified Water
Sodium Bicarbonate
Mannitol
Talcum
Magnesium Stearate
Croscarmellose Sodium
Colloidal Anhydrous Silica
Sodium Starch Glycolate
Colorcoat FC4SH
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30ºC

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture. Remove the tablets from the blister only directly prior to intake.

6.5 Nature and contents of container

10 Tablets are packed in one blister; such 3 blisters are packed in Unit carton along with Package Insert.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takki Health Care Limited,

A3 Royal Pearl Plaza,

Oppisite Our Lady Queen of Matrys catholic church Enoch Jarumi Road,

Sabon Lugbe, Abuja,

Nigeria.