SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

Product Name : Cilzec Plus Tablets (Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg USP)

Strength : 40 mg / 12.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg USP

Each uncoated bi-layered tablet contains:

Telmisartan USP	*40 mg*
Hydrochlorothiazide USP	12.5 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule shaped, uncoated, bi layered tablets, one layer with orange color and another layer with white to off white color having plain surface on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CILZEC PLUS tablets are indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

4.2 Posology and method of administration

Cilzec Plus should be taken once daily with liquid, with or without food in patients whose blood pressure is not adequately controlled by telmisartan alone. Individual dose titration with each of the two components is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see WARNINGS) of telmisartan are generally rare and apparently independent

of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose independent phenomena (e.g., pancreatitis), the former much more common than the latter.

Therapy with any combination of telmisartan and hydrochlorothiazide will be associated with both sets of dose independent side effects. Cilzec Plus (telmisartan and hydrochlorothiazide) tablets may be administered with other antihypertensive agents.

Patients with Renal Impairment

The usual regimens of Clizec plus, once daily may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so CILZEC PLUS tablets are not recommended.

Patients with Hepatic Impairment

CILZEC PLUS tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination.

4.3 Contraindications

CILZEC PLUS tablets are contraindicated in patients who are hypersensitive to any component of this product.

Telmisartan- Hypersensitivity to the active ingredient or any of other excipients Second and third trimesters of pregnancy and lactation Biliary obstructive disorders
Severe hepatic impairment

Hydrochlorothiazide – Hypersensitivity to thiazides and derivatives of sulfonamides, manifest gout, anuria, Addison's disease, hypercalcemia, hyperuricemia, severe renal and hepatic insufficiency

4.4 Special warnings and precautions for use

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in

the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, CILZEC PLUS tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of CILZEC PLUS tablets as soon as possible.

If oligohydramnios is observed, CILZEC PLUS tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume-Depleted Patients

Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g, in patients treated vigorously with diuretics, should only be approached cautiously. These conditions

should be corrected prior to administration of Cilzec Plus (telmisartan and hydrochlorothiazide) tablets. Treatment should be started under close medical supervision .
If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide

Hepatic Impairment: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations offluid and electrolyte balance may precipitate hepatic coma.

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

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

PRECAUTIONS

Serum Electrolytes

Telmisartan and Hydrochlorothiazide

No discontinuations due to hypokalemia reported during treatment with the telmisartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures,

muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient. If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying outtests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. CILZEC PLUS (telmisartan and hydrochlorothiazide) tablets should therefore be used with caution in these patients.

Impaired Renal Function

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin- aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan. There has been no long-term use of telmisartan in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Dual Blockade of the Renin-angiotensin-aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported.

Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE- inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under- digitalization.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Because lithium should not be used with diuretics, the use of lithium with telmisartan and hydrochlorothiazide is not recommended.

Ramiprif and Ramiprilat: When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combined use is not recommended.

Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (IN).

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19.

Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, exceptfor possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics: Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and co/estipol resins: Absorption of hydrochlorothi-azide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Cilzec Plus (telmisartan and hydrochlorothiazide) tablets.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing and thiazide diuretics.

Therefore, when CILZEC PLUS tablets and non-steroidal antiinflammatory agents re used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

4.6 Pregnancy and lactation

Pregnancy

(see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Thiazides appear in human milk.

Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into accountthe importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness and safety of telmisartan/ hydrochlorothiazide were observed in geriatric patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking anti hypertensive therapy.

4.8 Undesirable effects

The following adverse events were reported at a rate of 2% or greater in patients treated with telmisartan/hydrochlorothiazide, but were as, or more common in the placebo group: pain, headache, cough, urinary tract infection.

The following adverse events were reported at a rate less than 2% in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo: back pain, dyspepsia, vomiting, tachycardia, hypokalemia, bronchitis, pharyngitis, rash, hypotension postural, abdominal pain.

Adverse events occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

Telmisartan

Other adverse experiences that have been reported with telmisartan, without regard to causality, are listed below:

Autonomic Nervous System: impotence, increased sweating, flushing Body as a Whole: allergy, fever, leg pain, malaise, chest pain

Cardiovascular: palpitation, dependent edema, angina pectoris, leg edema, abnormal ECG, hypertension, peripheral edema.

CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia

Gastrointestinal: flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders

Metabolic: gout, hypercholesterolemia, diabetes mellitus

Musculoskeletal: arthritis, arthralgia, leg cramps, myalgia

Psychiatric: anxiety, depression, nervousness

Resistance Mechanism: infection, fungal infection, abscess, otitis media

Respiratory: asthma, rhinitis, dyspnea, epistaxis

Skin: dermatitis, eczema, pruritus

Urinary: micturition frequency, cystitis

Vascular: cerebrovascular disorder

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache A single case of angioedema was reported (among a total of 3781 patients treated with telmisartan).

Hydrochlorothlazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia

4.9 Overdose

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis.

If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase I). Angiotensin II is the principal press or agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II

synthesis. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the anti hypertensive effect of thiazides is not fully understood.

5.2 Pharmacokinetic properties

General

Telmisartan

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUG) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax andAUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan

with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Elimination

Telmisartan

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11 % of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61 % oflhe oral dose is eliminated as unchanged drug within 24 hours.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and a1-acid glycoprotein.

Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide, Povidone, Polysorbate, Mannitol, Purified water, Magnesium Stearate, Lactose Monohydrate, Microcrystalline Cellulose PH 102, Lake Sunset Yellow, Povidone Purified water, Sodium Starch Glycolate (Type A), Lake sunset yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Keep out of reach of children

Protect from light and moisture

Store below 30^{o}C in a dry place

6.5 Nature and contents of container

Cilzec Plus is available as pack of 3x10's

6.6 Special precautions for disposal and other handling

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

7. APPLICANT/HOLDER OF CERTIFICATE F PRODUCT REGISTRATION

Mega Lifesciences Nigeria Limited

6B, Guinness Road, Ogba, Ikeja, Lagos,

8. DRUG PRODUCT MANUFACTURER

Manufactured by:

MSN Laboratories Private Limited

(Formulation Division) Plot No.: 42, Anrich Industrial Estate,

Bollaram, Sangareddy District, - 502 325, Telangana, India

9. NAFDAC REGISTRATION NUMBER

A4-6823