SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

Product Name **:** Cilzec 40 Tablets (Telmisartan USP 40 mg)

Strength **:** 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Telmisartan USP 40 mg

Each uncoated tablet contains:

Telmisartan USP 40 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to off-white colored round shaped smooth flat bevel edged plain both sides uncoated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Telmisartan tablets are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

4.2 Posology and method of administration

Dosage must be individualized. The usual starting dose of Cilzec tablets is 40 mg once a day. Blood pressure response is dose related over the range of 20-80 mg

Special Populations:

Patients with depletion of intravenous volume should have the condition corrected or Telmisartan tablets should be initiated under close medical supervision patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision.

Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional blood pressure reduction beyond that achieved with 80 mg. Telmisartan tablet is required, a diuretic may be added. No initial

dosing adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored. Telmisartan tablets may be administered with other antihypertensive agents. Telmisartan tablets may be administered with or without food.

4.3 Contraindications

Telmisartan tablets are contraindicated in patient who are hypersensitive to any component of the product.

4.4 Special warnings and precautions for use

Fetal/Neonatal Morbidity and Mortality

Drug 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, Telmisartan 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.Olygohydramnios has been reported, presumably resulting from decreased fetal renal function; oligohydraminos in this setting has been associated with fetal limb contractures, craniofacialde formation 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.

There is no clinical experience with the use of Telmisartan tablets in pregnant women. No teratogenic effects were observed when Telmisartan was administered to pregnant rats at oral doses of up to 50mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with material toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis]. In rats, maternally toxic (reduction in bodyweight gain and food consumption) Telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m2 basis), administered during late gestation and location, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain.

Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m2basis, the maximum recommended human dose of Telmisartan (80 mg/day).

Hypotension in volume-Depleted Patients

In patients with an activated renin-angeotensin system, such as volume and/or salt-depleted patients (e.g. those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan tablets. This condition should be corrected prior to administration of Telmisartan tablets, or treatment should start under close medical supervision with a reduced dose.

If a hypotension dose occurs, the patient 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.

Precautions

General

Impaired Hepatic Function*:* 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. Telmisartan tablets should be used with caution in these patients.

Impaired Renal Function**:** 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 tablets.

Dual Blockade of the Renin-angiotensin-aldosterone system: As a consequence of inhibiting the renin angiotensinaldosterone system, changes in renal function (including actual 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 be used with caution and should include close monitoring of renal function.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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 (INR).

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 for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

4.6 Pregnancy and lactation

Pregnancy

Fetal/ Neonatal Morbidity and Mortality. (See Warning)

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.

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 account the 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 were observed in elderly patients compared to younger patients.

4.7 Effects on ability to drive and use machines

There are no data to suggest that Telmisartan affects the ability to drive and use machines. However, when driving or operating machinery it should be taken into account that with antihypertensive therapy, occasionally dizziness or drowsiness may occur.

4.8 Undesirable effects

Adverse events like back pain, sinusitis, diarrhea, pharyngitis occurred at an incidence of 1% or more in patients treated with Telmisartan and at a great rate than in patients treated with Telmisartan and at a greater rate then in patients treated with placebo, irrespective of their casual association.

In addition, the following events occurred at a rate of 1% but were at least as frequent in the placebo group; influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema. The incidence of adverse events is not dose-related and not correlated with gender, age, or race of patients. The incidence of cough occurring with Telmisartan was identical to that noted for placebo treated patients (1.6%).

4.9 Overdose

Limited data are available with regards to overdosage in humans. The most likely manifestation of overdosage with Telmisartan tablets 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal processor agent of the reninangiotensin 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 to the AT1

receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathway for angiotensin II synthesis. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular hemostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 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 inhibitor also inhibit the degradation of bradykinin , a reaction also catalyzed by ACE. Because Telmisartan does not inhibit ACE (Kinase II), it dose 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 receptor 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 rennin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of Telmisartan on blood pressure.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, peak concentrations (Cmax) of Telmisartan are reached in 0.51 hour after dosing.

Food slightly reduces the bioavailability of Telmisartan, with a reduction in the area under the plasma concentration-time cure (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose.

The absolute bioavailability of Telmisartan of Telmisartan is dose dependent.

At 40 and 160mg the bioavailability was 42% and 58%, respectively.

The pharmacokinetics of orally administered Telmisartan Telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) 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.

Metabolism and Elimination : Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the gluconoride of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of Telmisartan.

Distribution: Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1-acid glycoprotein, plasma 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.

Special Populations

Pediatric: Telmisartan pharmacokinetics have been investigated in patients<18 years of age.

Geriatric: The pharmacokinetics of Telmisartan does not differ between the elderly and those younger than 65 years.

Gender: Plasma concentration of Telmisartan is generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of Telmisartan are increased and absolute bioavailability approaches 100%.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose PH 101 , Croscarmellose Sodium , Meglumine , Poloxamer 188 , Povidone K-30 , Isopropyl Alcohol, Microcrystalline cellulose PH 102 , Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 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 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

(Formulations Division)

Plot No.: 42, Anrich Industrial Estate,

Bollaram, Sangareddy District, - 502 325,

Telangana, India

9. NAFDAC REGISTRATION NUMBER

A4-5522