WARNING
FETAL TOXICITY

- **When pregnancy is detected, discontinue Olmesartan as soon as possible**.
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.**

For the use of a Registered Medical Practitioner only

1. GENERIC NAME AND BRAND NAME

Olmesartan Medoxomil, Amlodipine Besylate & Hydrochlorothiazide Tablets

WINBP® - TRIO 20

2. QUALITATIVE & QUANTITATIVE COMPOSITION:

Each film coated tablet contains:
Olmesartan Medoxomil I.P. 20mg
Amlodipine Besylate I.P. Eq. to Amlodipine 5mg
Hydrochlorothiazide I.P. 12.5mg
Colours: Red Oxide of Iron, Yellow Oxide of Iron, Black Oxide of Iron & Titanium dioxide IP

3. DOSAGE FORM & STRENGTH:

Refer section 1 & 2

4. CLINICAL PARTICULARS:

4.1 THERAPEUTIC INDICATION

Treatment of essential hypertension.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adult Hypertension

Dosage must be individualized. The usual recommended starting dose of WIN BP TRIO is one tablet once a day

4.3 Contraindications

- Do not co-administer aliskiren with WIN BP TRIO in patients with diabetes.
- Severe bradycardia, cardiogenic shock, second or third degree heart block, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place)
- Hypersensitivity to the active substances Olmesartan or metoprolol or hydrochlorothiazide or to any of the excipients.
- Pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment
- Anuria
- The concomitant use of Olmesartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE

Morbidity in Infants

For hypertension, children < 1 year of age must not receive WIN BP. Drugs that act directly on the renin-angiotensin aldosterone system (RAAS) can have effects on the development of immature kidneys.

Hypotension in Volume- or Salt-Depleted Patients

Symptomatic hypotension may be anticipated after initiation of treatment with WIN BP TRIO, in patients with an activated renin-angiotensin aldosterone system, such as volume and/or salt-depleted patients (e.g., those being treated with high doses of diuretics). Initiate treatment under close medical supervision. Place the patient in the supine position if hypotension does occur, and, if necessary, give 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.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with heart failure, on renal replacement therapy, with advanced renal impairment, or on potassium supplements, potassium-containing salt substitutes, potassium-sparing diuretics, or other drugs that increase potassium levels. Periodic determinations of serum electrolytes should be done to detect possible electrolyte imbalances, particularly in patients at risk.

Impaired Renal Function

Changes in renal function may be anticipated in susceptible individuals treated with WIN BPTRIO as a consequence of inhibiting the renin-angiotensin-aldosterone system. Treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, in patients whose renal function may depend upon the activity of the renin-angiotensin aldosterone system (e.g., patients with severe congestive heart failure). In patients treated with WIN BP, similar results may be anticipated.

Sprue like enteropathy

Olmesartan can cause intestinal problems known as sprue-like enteropathy. Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization .If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

Hyperuricemia

Certain patients receiving thiazide diuretics, may be precipitated Hyperuricemia or acute gout.

Parathyroid Disease

Thiazides decrease calcium excretion and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia.

Electrolyte and Fluid Balance Status

Clinically significant hypokalemia is less common in patients who received 12.5 mg of hydrochlorothiazide than in patients who received higher doses. Measurement of serum electrolytes should be performed in patients who may be at risk for the development of hypokalemia. Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia and hypomagnesemia.

Symptoms of fluid and electrolyte imbalance include thirst, weakness, lethargy, dryness of mouth, drowsiness, restlessness, muscle pains or cramps, hypotension, oliguria, muscular fatigue, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop Interference with adequate oral electrolyte or brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroid or adrenocorticotropic hormone (ACTH) or after prolonged therapy. Hypokalemia may treated by potassium supplementation or increased intake of potassium rich foods.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide is a sulphonamide which can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include ocular pain or acute onset of decreased visual acuity and typically occur within hours to weeks of initiation of drug. Risk factors for developing acute angle-closure glaucoma may include a history of penicillin or sulfonamide allergy. Untreated acute angle-closure glaucoma can lead to permanent vision loss. Discontinue hydrochlorothiazide as rapidly as possible as the primary treatment. Consider immediate medical or surgical treatments if the intraocular pressure remains uncontrolled.

Diabetes and Hypoglycemia

Thiazide may cause manifestation of latent diabetes mellitus and these patients may require adjustment of their insulin dose.

Hepatic Impairment

In patients with moderate hepatic impairment compared to those in matched controls increases in AUC0-∞ and Cmax were observed, with an increase in AUC of about 60%. For patients with moderate to marked hepatic dysfunction, no initial dosage adjustment is recommended.

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic impairment.

Renal Impairment

Patients with renal insufficiency have elevated serum concentrations of olmesartan compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min). For patients with moderate to marked renal impairment (creatinine clearance <40 mL/min), no initial dosage adjustment is recommended.

Cumulative effects of the thiazides such as precipitate azotemia may develop in patients with impaired renal function.

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of Amlodipine particularly in patients with severe obstructive coronary artery disease.

4.5 DRUG INTERACTIONS

Olmesartan

No	Drug	Drug interaction	Remark
1	Digoxin	No significant drug interactions were reported	
2.	Warfarin	No significant drug interactions were reported	
3.	Antacids	The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [Al(OH)3/Mg(OH)2]	
4.	Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)	In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including olmesartanmedoxomil, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of angiotensin II receptor antagonists, including olmesartanmedoxomil may be attenuated by NSAIDs including selective COX-2 inhibitors.	Monitor renal function periodically in patients receiving olmesartanmedoxomil and NSAID therapy.

Amlodipine

Drug	*Drug interaction*	*Remark*
Sildenafil	When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.	Monitor blood pressure
Simvastatin	When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.	Monitor blood pressure
Simvastatin	A 77% increase in exposure to simvastatin compared to simvastatin alone.	Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
CYP3A4 Inhibitors	Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.	Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers	No information is available on the quantitative effects of CYP3A4 inducers on amlodipine.	Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.
Cyclosporine	40% increase in trough cyclosporine levels when concomitantly treated with amlodipine	

Hydrochlorthiazide

Alcohol, barbiturates, or narcotics	Potentiation of orthostatic hypotension may occur with thiazides	
Antidiabetic drugs (oral agents and insulin)		Dosage adjustment of the antidiabetic drug may be required when given concomitantly with thiazides
Cholestyramine and colestipol resins	Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively	
Corticosteroid, ACTH	Thiazide intensified electrolyte depletion, particularly hypokalemia.	
Pressor amines (e.g., norepinephrine)	Possible decreased response to pressor amines with thiazides	Not sufficient to preclude their use.
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)	Possible increased responsiveness of thiazides to the muscle relaxant	

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy

Pregnancy Category D

During the second and third trimesters of pregnancy, use of drugs that act on the renin-angiotensin system reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with skeletal deformations and fetal lung hypoplasia. Potential neonatal adverse effects include anuria, skull hypoplasia, hypotension, renal failure, and death. When pregnancy is detected, as soon as possible discontinue WIN BP TRIO.

No adequate and well-controlled studies in pregnant women, Hydrochlorothiazide should be used during pregnancy only if clearly needed.

Amlodipine is a pregnancy category C drug.In the second and third trimester of pregnancy, these adverse outcomes are usually associated with use of these drugs. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other

antihypertensive agents. During pregnancy, appropriate management of maternal hypertension is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. To assess the intra-amniotic environment, perform serial ultrasound examinations. If oligohydramnios is observed, unless it is considered lifesaving for the mother, discontinue WIN BP TRIO. Based on the week of pregnancy, Fetal testing may be appropriate. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to WIN BP TRIOfor hypotension, oliguria, and hyperkalemia.

Nursing Mothers

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother because of the potential for adverse effects on the nursing infant.

Thiazides are excreted in breast milk. As there is potential for adverse effects on the nursing infant, it should be decided whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Neonates with a history of in utero exposure to olmesartan

If hypotension or oliguria occurs, direct attention toward support of blood pressure and renal perfusion, exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

In children < 6 years of age, olmesartan has not been shown to be effective for hypertension.

In kidney development, the renin-angiotensin aldosterone system (RAAS) plays a critical role. RAAS blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the reninangiotensin aldosterone system (RAAS) can alter normal renal development.

Geriatric Use

No differences were observed between elderly patients and younger patients in effectiveness or safety when they were treated with olmesartan. 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.

Start treatment with the lowest available dose of hydrochlorothiazide (12.5 mg) in elderly as there is increase in side effects. Further titration should be done in 12.5 mg increments.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: **A**mlodipine can have minor or moderate influence on the ability to drive and use machines. When driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.
Olmesartan

Hydrochlorthiazide

4.8 UNDESIRABLE EFFECTS:

Body as a Whole: Peripheral edema, chest pain

Gastrointestinal: abdominal pain, gastroenteritis, dyspepsia, nausea, anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

Metabolic and Nutritional Disorders: hyperlipemia, hypercholesterolemia, hyperuricemia

Central and Peripheral Nervous System: vertigo, somnolence, sexual dysfunction (maleand female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, insomnia, paresthesia, involuntary muscle contractions, migraine, hypoesthesia

Cardiovascular: tachycardia, arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.

Musculoskeletal: arthritis, arthralgia, myalgia

Skin and Appendages: rash

Post-Marketing Experience

Body as a Whole: Asthenia, anaphylactic reactions, angioedema, edema , flushing, allergy, weakness, leg pain, malaise, fever

Gastrointestinal: Vomiting, sprue-like enteropathy , jaundice and hepatic enzyme elevations, flatulence, constipation, pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, sialadenitis, cramping, nausea, anorexia, gastroesophageal reflux, toothache, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, nonspecific gastrointestinal disorders, gingival hypertrophy

Metabolic and Nutritional Disorders: Hyperkalemia

Musculoskeletal: Rhabdomyolysis
Urogenital System: Increased blood creatinine levels, acute renal failure , micturition frequency, micturition disorder, nocturia, impotence., micturition frequency, cystitis

Skin and Appendages: Alopecia, urticaria, pruritus

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Respiratory System: dyspnea, epistaxis, asthma, bronchitis, rhinitis

Skin and Appendages: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.

Autonomic Nervous System: dry mouth, sweating increased.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

Renal: Renal failure, interstitial nephritis, renal dysfunction

Others: gynecomastia.

4.9 OVERDOSE:

Related to overdosage in humans, limited data are available.

The most likely manifestations of overdosage would be tachycardia and hypotension; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. Initiate supportive treatment if symptomatic hypotension occurs. The dialyzability of olmesartan is unknown.

If massive overdose occurs , initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are required . If hypotension occurs, cardiovascular support including elevation of the extremities and the judicious administration of fluids is required. If hypotension is unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Symptomatic and supportive measures should be employed, in the event of overdosage of Hydrochlorthiazide. Gastric lavage performed or Emesis should be induced. The other established procedures are correct dehydration, electrolyte imbalance, hepatic coma and hypotension. Oxygen or artificial respiration for respiratory impairment may be given if required. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5. PHARMACOLOGIC PROPERTIES

5.1 MECHANISM OF ACTION

Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

Hydrochlorthiazide: The acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect. A direct vasodilatory mechanism has also been proposed

5.2 PHARMACODYNAMIC PROPERTIES:

<u>Olmesartan:</u>
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor 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. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity 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 a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because Olmesartan Medoxomil does not inhibit ACE (kininase II), it does not affect the response to bradykinin. The clinical relevance of this fact is not yet known. 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 circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure. The pressor effects of angiotensin I infusion are inhibited by olmesartan

Amlodipine:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. Amlodipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle and causes a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise. Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles

Hydrochlorthiazide:
The acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect. A direct vasodilatory mechanism has also been proposed. Plasma volume returns toward normal, with chronic administration, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is unknown.
Thiazides are not effective on normal blood pressure. Onset of action occurs within 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

5.3 PHARMACOKINETIC PROPERTIES

	Olmesartan medoxomil	**Amlodipine**	**Hydrochlorothiazide**
Absorption	During absorption, Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan from the gastrointestinal tract. The absolute bioavailability of olmesartan is approximately 26%.	Amlodipine absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The absorption of amlodipine is not affected by food.	Well absorbed (65% to 75%) following oral administration. Absorption is reduced in patients with congestive heart failure. Peak plasma concentrations are

	After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.		observed within 1 to 5 hours of dosing. Plasma concentrations are linearly related to the administered dose.
Distribution	The volume of distribution of olmesartan is approximately 17 L.	Amlodipine is well distributed to the heart and vasculature	When administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.
Metabolism & Excretion	Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.	Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism 10% of the parent compound and 60% of the metabolites excreted in the urine	Concentrations are 1.6 to 1.8 times higher in whole blood than in plasma. Eliminated primarily by renal pathways. Following oral doses 55% to 77% appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged
Half life	Approximately 13 hours	The terminal elimination half-life is about 30–50 hours	The plasma elimination half-life has been reported to be 6 to 15 hours
Plasma Protein Binding	Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells.	93% of the circulating drug is bound to plasma proteins	Approximately 40% to 68%

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

The rationale for no or limited new toxicity from the triple combination of olmesartan medoxomil, amlodipine, and hydrochlorothiazide has already been established on the basis of the safety profile

of the individual compounds or the dual combinations. To clarify the toxicological profile, a 3-month repeated dose toxicity study was conducted in rats, and the results demonstrated that the combined administration of olmesartan medoxomil, amlodipine, and hydrochlorothiazide neither augment any existing toxicities of the individual agents nor induce any new toxicities and there were no toxicologically synergistic effects observed in the study.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide. However, these studies have been conducted for olmesartan medoxomil, amlodipine and hydrochlorothiazide alone.

Olmesartan was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m2 basis, about 480 times the MRHD of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (on a mg/m2 basis, about 120 times the MRHD of 40 mg/day), revealed no evidence of a carcinogenic effect of olmesartan.

Both olmesartan medoxomil and olmesartan tested negative in the in vitro Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung) and tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. Olmesartan medoxomil tested negative in vivo for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan at dose levels as high as 1000 mg/kg/day (240 times the MRHD of 40 mg/day on a mg/m2 basis) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating. (Calculations based on a 60 kg patient.)

Rats and mice treated with amlodipine maleate in the diet for up to 2 years, at concentrations calculated to provide daily dosage levels of amlodipine 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the MRHD of amlodipine 10 mg/day. For the rat, the highest dose was, on a mg/m2 basis, about two times the MRHD (calculations based on a 60 kg patient).

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

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 amlodipine up to 10 mg/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m2 basis).

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). These doses in mice and rats are about 117 and 39 times, respectively, the MRHD of 25 mg/day on a mg/m2 basis. (Calculations based on a 60 kg patient.) The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic in vivo in assays using mouse germinal cell chromosomes, Chinese Hamster bone marrow chromosomes, or in Drosophilla sex-linked recessive lethal trait gene. Positive test results were obtained in the in vitro CHO Sister

Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay and the Aspergillus nidulans nondisjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses in mice and rats are about 19 and 1.5 times, respectively, the MRHD of 25 mg/day on a mg/m2 basis. (Calculations based on a 60 kg patient.)

Developmental Toxicity

No reproductive studies have been conducted with the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide. However, these studies have been conducted for olmesartan medoxomil, amlodipine and hydrochlorothiazide alone, and olmesartan medoxomil and hydrochlorothiazide together.

No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose [MRHD] on a mg/m2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal

to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricular, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

No teratogenic effects were observed when 1.6:1 combinations of olmesartan medoxomil and hydrochlorothiazide were administered to pregnant mice at oral doses up to 1625 mg/kg/day (122 times the MRHD on a mg/m2 basis) or pregnant rats up to 1625 mg/kg/day (243 times the MRHD on a mg/m2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (0.3 times the MRHD on a mg/m2 basis). In rats, however, fetal body weights at 1625 mg/kg/day (a toxic, sometimes lethal dose in the dams) were significantly lower than control. The no observed effect dose for developmental toxicity in rats is 162.5 mg/kg/day, about 24 times, on a mg/m2 basis, the MRHD of 40 mg olmesartan medoxomil/25 mg hydrochlorothiazide/day. (Calculations based on a 60 kg patient.)

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively about 10 and 20 times the maximum recommended human dose of 10 mg amlodipine on a mg/m2 basis) during their respective periods of major organogenesis (calculations based on a patient weight of 60 kg). However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestational period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

7. DESCRIPTION:

WINBP - TRIO 20 is supplied for oral administration, as a film coated tablet of Olmesartan Medoxomil, Amlodipine Besylate & Hydrochlorothiazide. Each film coated tablet of WINBP - TRIO 20 contains Olmesartan Medoxomil 20mg, Amlodipine Besylate equivalent to Amlodipine 5mg, Hydrochlorothiazide 12.5mg.

8. PHARMACEUTICAL PARTICULARS:

8.1 Incompatibilities

Not Applicable

SHELF-LIFE

Refer pack

PACKAGING INFORMATION

Refer Pack

STORAGE CONDITION AND HANDLING INSTRUCTIONS

Refer Pack

9. PATIENT COUNSELLING INFORMATION

Instruct patients on the risk of foetal harm when this drug is used in pregnancy [see Warnings and Precautions and Use in Specific Populations]. Advise patients to immediately contact their healthcare provider if they develop rash or with the use of any other prescription or non-prescription medication or herbal products along with this drug.

10. DETAILS OF MANUFACTURER:

Refer Pack for manufacturer details.

MARKETED BY:

Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER

Refer Pack for Permission/License details

12. DATE OF REVISION:

Version 4.0 dated 20th Nov 2023