Module –1 ADMINISTRATIVE INFORMATION
Drug Product: OLMECURE-CT 20 (OLMESARTAN MEDOXOMIL WITH CHLORTHALIDONE TABLETS)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

1.1 **Product Name :** OLEMCURE-CT 10

1.2 **Strength :** 20 mg and 12.5 mg per Tablet

1.3 **Pharmaceutical Dosage Form :** Uncoated tablet

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Olemesartan Medoximil with Chlortalidone Tablets

2.2 Quantitative Declaration

EACH UNCOATED TABLET CONTAINS:

OLMESARTAN MEDOXOMIL BP…….20 MG

CHLORTHALIDONE BP…….12.5 MG

EXCIPIENTS……QS

Module –1 ADMINISTRATIVE INFORMATION
Drug Product: OLMECURE-CT 20 (OLMESARTAN MEDOXOMIL WITH CHLORTHALIDONE TABLETS)
Quantitative Composition Formula:

Batch Size: 1,00,000 Tablets

Sr. No.	Ingredients	Specification	Quantity / Tablet (mg or mL)	% Overages	Quanity for 1,00,000 tablets (Kg/Ltr.)
Granulation					
1.	Olmesartan Medoxomil	BP	20.000	-	2.000
2.	Lactose Monohydrate	BP	65.000	-	6.500
3.	Microcrystalline Cellulose	BP	50.000	-	5.000
4.	Cross Povidone	BP	10.000	-	1.000
5.	Hydroxy Propyl Celluslose	BP	2.000	-	0.200
6.	Colloidal Silicone Dioxide	USP	1.5000	-	0.150
7.	Chlorthalidone	BP	12.500	-	1.250
Wet Granulation					
8.	Povidone K-30 (PVPK-30)	BP	5.000		0.500
9.	Iso Propyl Alchohol	BP	0.1 mL		10.000 Ltr
Lubrication					
10.	Microcrystalline Cellulose	BP	21.000		2.100
11.	Colloidal Silicon Dioxide	USP	2.000		0.200
12.	Magnesium Stearate	BP	5.000		0.500
13.	Cross Providone	BP	5.000		0.500
14.	Purified Talc	BP	3.000		0.300
Compressed Tablet Weight			202.000 mg		

Module –1 ADMINISTRATIVE INFORMATION
Drug Product: OLMECURE-CT 20 (OLMESARTAN MEDOXOMIL WITH CHLORTHALIDONE TABLETS)
3. Pharmaceutical form:

White Coloured Round Shaped,Biconvex Uncoated Tablet having Both Side Plain..

4. Clinical Particulars

4.1. Therapeutic indications:

Olmesartan Medoxomil:

Treatment of essential hypertension.

Treatment of hypertension in children and adolescents from 6 to less than 18 years of age

Chlorthalidone:

Is indicated in the management of hypertension either alone or

in combination with other antihypertensive drugs.

Chlorthalidone is indicated as adjunctive therapy in edema associated with congestive heart

failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Chlorthalidone has also been found useful in edema due to various forms of renal dysfunction

such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure

4.2. Posology and method of administration:

Posology

Olmesartan Medoxomil:

Adults

The recommended starting dose of Olmesartan Medoxomil is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of Olmesartan Medoxomil may be increased to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, Olmesartan Medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.

The antihypertensive effect of Olmesartan Medoxomil is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose regimen for any patient.

Elderly (65 years or older)

No adjustment of dosage is generally required in older people If up-titration to the maximum dose of 40mg daily is required, blood pressure should be closely monitored.

Renal impairment

The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20 – 60 mL/min) is 20 mg Olmesartan Medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of Olmesartan Medoxomil in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended, since there is only limited experience in this patient group.

Hepatic impairment

No adjustment of dosage recommendations is required for patients with mild hepatic impairment. In patients with moderate hepatic impairment, an initial dose of 10 mg Olmesartan Medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of Olmesartan Medoxomil in patients with severe hepatic impairment, therefore use is not recommended in this patient group Olmesartan Medoxomil should not be used in patients with biliary obstruction.

Paediatric population

Children and adolescents from 6 to less than 18 years of age

The recommended starting dose of olmesartan medoxomil in children from 6 to less than 18 years of age is 10 mg olmesartan medoxomil once daily. In children whose blood pressure is not adequately controlled at this dose, the dose of olmesartan medoxomil may be increased to 20 mg once daily. If additional blood pressure reduction is required, in children who weigh > 35 kg, the olmesartan medoxomil dose may be increased to a maximum of 40 mg. In children who weigh < 35 kg, the daily dose should not exceed 20 mg.

Other paediatric population

The safety and efficacy of olmesartan medoxomil in children and aged 1 to 5 years old have not yet been established.

Olmesartan Medoxomil should not be used in children below 1 years of age because of safety concerns and lack of data in this age group.

Method of administration:

In order to assist compliance, it is recommended that Olmesartan Medoxomil be taken at about the same time each day, with or without food, for example at breakfast time. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed.

Chlorthalidone:

Usage in Pregnancy

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and foetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of developed toxaemia. Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Chlorthalidone is indicated in pregnancy when edema is due to pathologic causes just as it is in the absence of pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary.

There is hypervolemia during normal pregnancy that is harmful to neither the foetus nor the mother (in the absence of cardiovascular disease) but that is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort that is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate

Method of administration

Tablets for oral use.

4.3. Contra-indications:

Olmesartan Medoxomil

Intravascular volume depletion:

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Olmesartan Medoxomil.

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 other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.

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.

Renal impairment and kidney transplantation:

When Olmesartan Medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of Olmesartan Medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min). There is no experience of the administration of Olmesartan Medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (ie creatinine clearance <12 mL/min).

Hepatic impairment:

There is no experience in patients with severe hepatic impairment and therefore use of Olmesartan Medoxomil in this patient group is not recommended.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

The risk, that may be fatal, is increased in older people, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the rennin angiotensin - aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes, renal impairment, age (> 70 years)

- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-

inflammatory drugs (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim.

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g, acute limb ischemia, rhabdomyolysis, extended trauma).

Close-monitoring of serum potassium in at risk patients is recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Lithium:

As with other angiotensin-II receptor antagonists, the combination of lithium and Olmesartan Medoxomil is not recommended.

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:

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

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmesartan Medoxomil is not recommended in such patients.

Sprue-like enteropathy:

In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking Olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with Olmesartan, and in the absence of other apparent etiologies, Olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.

Ethnic differences:

As with all other angiotensin II antagonists, the blood pressure lowering effect of Olmesartan Medoxomil is somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

Pregnancy:

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

Other:

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

Pregnancy

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 antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Angiotensin II antagonists therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II 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 antagonists should be closely observed for hypotension

Breastfeeding

Olmesartan is excreted in the milk of lactating rats but it is not known whether Olmesartan is excreted in human milk. Because no information is available regarding the use of Olmesartan Medoxomil during breast-feeding, Olmesartan Medoxomil is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant

Chlorthalidone:

Known hypersensitivity to chlorthalidone or other sulfonamide-derived drugs

4.4. Special warning and precautions for use: -

Olmesartan Medoxomil

Intravascular volume depletion:

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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 other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.

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Hepatic impairment:

There is no experience in patients with severe hepatic impairment and therefore use of Olmesartan Medoxomil in this patient group is not recommended.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

The risk, that may be fatal, is increased in older people, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the rennin angiotensin - aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes, renal impairment, age (> 70 years)

- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim.

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If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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Ethnic differences:

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Pregnancy:

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

Other:

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

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Chlorthalidone:

Should be used with caution in severe renal disease. In patients with renal disease, chlorthalidone or related drugs may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease, because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

4.5 Interaction with other medicinal products and other forms of interactions:

Olmesartan Medoxomil

Paediatric population:

Interaction studies have only been performed in adults.

It is not known if the interactions in children are similar to those in adults.

Effects of other medicinal products on Olmesartan Medoxomil:

Other antihypertensive medications:

The blood pressure lowering effect of Olmesartan Medoxomil can be increased by concomitant use of other antihypertensive medications.

ACE-inhibitors, angiotensin II receptor blockers or aliskiren:

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.

Potassium supplements and potassium sparing diuretics:

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium sparing diuretics, potassium supplements, salt substitutes containing

potassium or other drugs that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium (see section 4.4). Such concomitant use is therefore not recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses > 3g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

Bile acid sequestering agent colesevelam:

Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of Olmesartan and reduces t1/2. Administration of Olmesartan Medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering Olmesartan Medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered.

Other compounds:

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of Olmesartan was observed. Coadministration of warfarin and digoxin had no effect on the pharmacokinetics of Olmesartan.

Effects of Olmesartan Medoxomil on other medicinal products:

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore use of Olmesartan Medoxomil and lithium in combination is not recommended If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other compounds

Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminium hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular Olmesartan Medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Olmesartan had no clinically relevant inhibitory effects on in vitro human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal inducing effects on

rat cytochrome P450 activities. Therefore in vivo interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between Olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected

Chlorthalidone:

Chlorthalidone may add to or potentiate the action of other antihypertensive drugs.

Insulin requirements in diabetic patients may be increased, decreased or unchanged. Higher

dosage of oral hypoglycaemic agents may be required.

Chlorthalidone and related drugs may increase the responsiveness to tubocurarine.

Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This

diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Lithium renal clearance is reduced by chlorthalidone, increasing the risk of lithium toxicity

4.6. Use in pregnancy and lactation:

Olmesartan Medoxomil

Pregnancy

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 antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Angiotensin II antagonists therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II 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 antagonists should be closely observed for hypotension

Breastfeeding

Olmesartan is excreted in the milk of lactating rats but it is not known whether Olmesartan is excreted in human milk. Because no information is available regarding the use of Olmesartan Medoxomil during breast-feeding, Olmesartan Medoxomil is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant

Chlorthalidone:

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of developed toxaemia. Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Chlorthalidone is indicated in pregnancy when edema is due to pathologic causes just as it is in the absence of pregnancy Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary.

There is hypervolemia during normal pregnancy that is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease) but that is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort that is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate

4.7. Effects on ability to drive and operate machine:

Olmesartan Medoxomil has minor or moderate influence on the ability to drive and use machines. Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react

4.8. Undesirable effects:

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Drug Product: OLMECURE-CT 20 (OLMESARTAN MEDOXOMIL WITH CHLORTHALIDONE TABLETS)
Olmesartan Medoxomil

Summary of the safety profile:

The most commonly reported adverse reactions during treatment with Olmesartan Medoxomil Tablets are headache (7.7%), influenza-like symptoms (4.0%) and dizziness (3.7%).

In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on Olmesartan Medoxomil and 0.9% on placebo).

The incidence was also somewhat higher on Olmesartan Medoxomil compared with placebo for hypertriglyceridaemia (2.0% versus 1.1%) and for raised creatine phosphokinase (1.3% versus 0.7%).

Tabulated list of adverse reactions:

Adverse reactions from Olmesartan Medoxomil in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized in the below table.

The following terminologies have been used in order to classify the occurrence of adverse reactionsvery common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
Immune system disorders	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
Nervous system disorders	Dizziness	Common
	Headache	Common
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	Common
	Pharyngitis	Common

	Cough	Common
	Rhinitis	Common
Gastrointestinal disorders	Gastroenteritis	Common
	Diarrhoea	Common
	Abdominal pain	Common
	Nausea	Common
	Dyspepsia	Common
	Vomiting	UnCommon
	Sprue-like enteropathy	Very rare
Skin and subcutaneous tissue disorders	Exanthema	UnCommon
	Allergic dermatitis	UnCommon
	Urticaria	UnCommon
	Rash	UnCommon
	Pruritus	UnCommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Arthritis	Common
	Back pain	Common
	Skeletal pain	Common
	Myalgia	Common
	Muscle spasm	UnCommon
Renal and urinary disorders	Haematuria	Common
	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
General disorders and administration site conditions	Pain	Common
	Chest pain	Common
	Peripheral oedema	Common
	Influenza-like symptoms	Common

	Fatigue	Common
	Face oedema	UnCommon
	Asthenia	UnCommon
	Malaise	UnCommon
	Lethargy	Rare

Paediatric population

The safety of olmesartan was monitored in 361 children and adolescents, aged 1-17 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Epistaxis is a common adverse event in children (i.e. ≥ 1/100 to < 1/10) that has not been reported in adults.
- During the 3 weeks of double blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6-17 years of age in the high olmesartan dose group.
- The overall safety profile for olmesartan in paediatric patients does not differ significantly from the safety profile in adults.

Elderly (age 65 years or over)

In elderly people the frequency of hypotension is slightly increased from rare to uncommon.

Chlorthalidone

The following adverse reactions have been observed, but there is not enough systematic collection of data to support an estimate of their frequency. Gastrointestinal System Reactions: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. Central Nervous System Reactions: dizziness, vertigo, paresthesias, headache, xanthopsia. Hematologic Reactions: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. Dermatologic-Hypersensitivity Reactions: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Cardiovascular Reaction: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics

Other Adverse Reactions: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness,

restlessness, impotence.

Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn

4.9. Overdose:

Olmesartan Medoxomil:

Only limited information is available regarding overdosage in humans. The most likely effect of overdosage is hypotension. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of Olmesartan.

Clorthalidone:

Symptoms of acute overdosage include nausea, weakness, dizziness and disturbances of electrolyte balance. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

Therapy should be initiated with the lowest possible dose, then titrated according to individual patient response. A single dose given in the morning with food is recommended; divided doses are unnecessary

5. Pharmacological Properties

5.1. Pharmaco-dynamic properties:

Olmesartan Medoxomil:

Pharmacotherapeutic group: Angiotensin II antagonists and Diuretics, ATC code: C09C A 08..

Mechanism of action

Olmesartan Medoxomil is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the

angiotensin II (AT1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT1) receptor.

Clinical efficacy and safety

In hypertension, Olmesartan Medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after cessation of therapy.

Once daily dosing with Olmesartan Medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment. When used together with hydrochlorothiazide, the reduction in blood pressure is additive and coadministration is well tolerated.

The effect of Olmesartan on mortality and morbidity is not yet known.

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with Olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3.2 years, patients received either Olmesartan or placebo in addition to other antihypertensive agents, except ACE inhibitors or ARBs.

For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of Olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2% (178 of 2160) of the patients in the Olmesartan group and 9.8% (210 of 2139) in the placebo group developed microalbuminuria.

For the secondary endpoints, cardiovascular events occurred in 96 patients (4.3%) with Olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with Olmesartan compared to placebo treatment (15 patients (0.7%) vs. 3 patients (0.1%)), despite similar rates for non-fatal stroke (14 patients (0.6%) vs. 8 patients (0.4%)), non-fatal myocardial infarction (17 patients (0.8%) vs. 26 patients (1.2%)) and non-cardiovascular mortality (11 patients (0.5%) vs. 12 patients (0.5%)). Overall mortality with Olmesartan was numerically increased (26 patients (1.2%) vs. 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events.

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial Investigated the effects of Olmesartan on renal and cardiovascular outcomes in 577 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up

of 3.1 years, patients received either Olmesartan or placebo in addition to other antihypertensive agents including ACE inhibitors.

The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all cause death) occurred in 116 patients in the Olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (HR 0.97 (95% CI 0.75 to 1.24); p=0.791). The composite secondary cardiovascular endpoint occurred in 40 Olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5%) patients receiving Olmesartan versus 3 (1.1%) receiving placebo, overall mortality 19 (6.7%) versus 20 (7.0%), non-fatal stroke 8 (2.8%) versus 11 (3.9%) and non-fatal myocardial infarction 3 (1.1%) versus 7 (2.5%), respectively.

Paediatric population

The antihypertensive effects of Olmesartan Medoxomil in the paediatric population were evaluated in a randomized, double-blind, placebo-controlled study in 302 hypertensive patients aged 6 to 17 years. The study population consisted of an all-black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 blacks. The aetiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 mg (low dose) or 20 mg (high dose) of Olmesartan Medoxomil once daily and patients who weighed ≥35 kg were randomized to 5 mg (low dose) or 40 mg (high dose) of Olmesartan Medoxomil once daily. Olmesartan Medoxomil significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmesartan Medoxomil at both low and high doses significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from the baseline, respectively. This effect was also observed during the 2 weeks randomized withdrawal phase, whereby both mean systolic and diastolic blood pressures demonstrated a statistically significant rebound in the placebo group compared to Olmesartan group. The treatment was effective in both, paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥5 kg received 0.3 mg/kg of Olmesartan Medoxomil once daily for three weeks in an open label phase and then were randomized to receiving Olmesartan Medoxomil or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was 3/3 mmHg lower in the group randomized to Olmesartan Medoxomil; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/-1 to 7).

Clorthalidone:

Chlorthalidone increases the excretion of sodium, chloride, and water by inhibiting sodium ion transport across the renal tubular epithelium. Its primary site of action is in the cortical diluting segment of the ascending limb of the loop of Henle. Thiazides and related compounds also decrease the glomerular filtration rate, which further reduces the drug's efficacy in patients with renal

impairment. By increasing the delivery of sodium to the distal renal tubule, chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism. Hypokalaemia and hypochloraemia may cause mild metabolic alkalosis. However, the diuretic efficacy of chlorthalidone is not affected by the acid-base balance in the patient. Chlorthalidone is not an aldosterone antagonist, and its actions are independent of carbonic anhydrase inhibition.

Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Eventually, cardiac output returns to normal, and plasma and extracellular fluid volume return to slightly less than normal, but a reduction in peripheral vascular resistance is maintained, resulting in lower blood pressure. The reduction in plasma volume induces an elevation in plasma renin activity and aldosterone secretion, further contributing to the potassium loss associated with thiazide diuretic therapy. In general, diuretics worsen glucose tolerance and exert detrimental effects on the lipid profile

5.2. Pharmaco-kinetic properties:

Olmesartan Medoxomil

Absorption and distribution

Olmesartan Medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, Olmesartan, by esterase in the gut mucosa and in portal blood during absorption from the gastrointestinal tract.

No intact Olmesartan Medoxomil or intact side chain Medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of Olmesartan from a tablet formulation was 25.6%.

The mean peak plasma concentration (Cmax) of Olmesartan is reached within about 2 hours after oral dosing with Olmesartan Medoxomil, and Olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of Olmesartan and therefore Olmesartan Medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of Olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between Olmesartan and other highly bound coadministered drugs is low (as confirmed by the lack of a clinically significant interaction between

Olmesartan Medoxomil and warfarin). The binding of Olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29L).

Biotransformation and elimination

Total plasma clearance was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of 14C-labelled Olmesartan Medoxomil, 10 - 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed Olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as Olmesartan. No other significant metabolite was detected. Enterohepatic recycling of Olmesartan is minimal. Since a large proportion of Olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

The terminal elimination half-life of Olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 – 0.7 L/h and was independent of dose.

Paediatric population:

The pharmacokinetics of Olmesartan was studied in paediatric hypertensive patients aged 1 to 16 years. The clearance of Olmesartan in paediatric patients was similar to that in adult patients when adjusted by the body weight.

There is no pharmacokinetic information available in renally impaired paediatric subjects.

Elderly (age 65 years or older):

In hypertensive patients, the AUC at steady state was increased by ca 35% in elderly patients (65 – 75 years old) and by ca 44% in very elderly patients (≥ 75 years old) compared with the younger age group. This may be at least in part related to a mean decrease in renal function in this group of patients.

Renal impairment:

In renally impaired patients, the AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls.

Hepatic impairment:

After single oral administration, Olmesartan AUC values were 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of Olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment,

Olmesartan mean AUC was again about 65% higher than in matched healthy controls. Olmesartan mean Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan Medoxomil has not been evaluated in patients with severe hepatic impairment.

Drug interactions

Bile acid sequestering agent colesevelam:

Concomitant administration of 40 mg Olmesartan Medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in Cmax and 39% reduction in AUC of Olmesartan. Lesser effects, 4% and 15% reduction in Cmax and AUC respectively, were observed when Olmesartan Medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half-life of Olmesartan was reduced by 50 – 52% irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride.

Chlorthalidone:

Chlorthalidone is administered orally. The drug is 75% bound to plasma proteins and is also highly bound to red blood cells (blood to plasma ratio 72.5), with carbonic anhydrase as the binding site. Chlorthalidone crosses the placenta and is distributed into human breast milk. The onset of action is about 2 hours, with peak effects occurring in 2—6 hours and the duration of action lasting 48—72 hours. The majority of the drug is excreted unchanged in the urine (50—74%), with some potential biliary excretion. The mean half-life of chlorthalidone is approximately 40 to 60 hours.
Oral Route
Chlorthalidone is absorbed from the GI tract following oral administration, with a bioavailability of about 65%

5.3. Pre-clinical safety data:

In chronic toxicity studies in rats and dogs, Olmesartan Medoxomil showed similar effects to other AT1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT1 receptors); reduction in heart weight; a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of Olmesartan Medoxomil have also occurred in preclinical trials on other AT1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE inhibitors and other AT1 receptor antagonists, would appear to have no clinical relevance.

Like other AT1 receptor antagonists Olmesartan Medoxomil was found to increase the incidence of chromosome breaks in cell cultures in vitro. No relevant effects were observed in several in vivo studies using Olmesartan Medoxomil at very high oral doses of up to 2000 mg/kg. The overall

data of a comprehensive genotoxicity testing suggest that Olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan Medoxomil was not carcinogenic, neither in rats in a 2 year study nor in mice when tested in two 6 month carcinogenicity studies using transgenic models.

In reproductive studies in rats, Olmesartan Medoxomil did not affect fertility and there was no evidence of a teratogenic effect. In common with other angiotensin II antagonists, survival of offspring was reduced following exposure to Olmesartan Medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, Olmesartan Medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats, however, there was no indication of a fetotoxic effect.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity, or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18-times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate
Microcrystalline Cellulose
Cross Povidone
Hydroxy Propyl Celluslose
Colloidal Silicone Dioxide

Iso Propyl Alchohol
Magnesium Stearate
Purified Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in 30°C,Protect from light and Moisture

6.5 Nature and contents of container

3 Alu Alu Blister of 1 X 10 Tablet to be packed in Box with Packing Insert

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

Name of Person	-
Company Name	DOLOPHARMA
Address	P.O. BOX 102976 – 00101
Telephone No	254 732 608 221
Fax	-
Email	dolophc@gmail.com

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

OLMECURE-CT

OLMESARTAN MEDOXOMIL WITH CHLORTALIDONE TABLETS

COMPOSITION:

OLMECURE-CT 20

Each uncoated tablet contains:

Olmesartan Medoxomil BP	20mg.
Chlortalidone BP	12.5mg.
Excipients	Q.S

OLMECURE-CT 40

Each uncoated tablet contains:

Olmesartan Medoxomil BP	40mg.
Chlortalidone BP	12.5mg.
Excipients	Q.S
Colour: Brilliant Blue FCF	

PHARMACOKINETICS:

- **Absorption:**
  Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract.
  Chlortalidone has been formulated with PVP (povidone polyvinylpyrrolidone), a bioavailability enhancer that provides 104% to 116% bioavailability relative to an oral solution of Chlortalidone. Chlortalidone cannot be substituted with other formulations of chlortalidone.
- **Distribution:**
  Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses. In the blood, approximately 75% of the drug is bound to plasma proteins over a concentration range of 0.2 to 7.7 ug/mL.
  Chlortalidone In the blood, approximately 75% of the drug is bound to plasma proteins over a concentration range of 0.2 to 7.7 ug/mL.
- **Elimination:**
  Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. The mean plasma half-life of chlortalidone is about 40 to 60 hours. It is eliminated primarily as unchanged drug in the urine.

PHARMACODYNAMICS:

Olmesartan and chlortalidone which lower blood pressure effectively. Olmesartan is an angiotensin receptor blocker (ARB). It works by blocking the hormone angiotensin thereby relaxing blood vessels. This allows the blood to flow more smoothly and the heart to pump more efficiently. Chlortalidone is a diuretic that removes extra water and certain electrolytes from the body. Over time it also relaxes blood vessels and improves blood flow.

INDICATIONS AND USAGE:

Olmesartan Medoxomil + Chlortalidone Tablet is a combination of two medicines namely Olmesartan and chlortalidone. It is generally used when one medicine alone is not controlling your blood pressure effectively. Olmesartan works by relaxing and widening your blood vessels so your blood can flow more easily. This will lower your blood pressure. Chlortalidone is known as a diuretic (water pill) which increases urine output thereby lowering blood pressure. If your blood pressure is controlled you are less at risk of having a heart attack, stroke, or kidney problems. The medicine must be taken regularly as prescribed to be effective. You do not usually feel any direct benefit from taking this medicine, but it works in the long term to keep you well.

DOSAGE AND ADMINISTRATION:

- Initiate therapy with the lowest possible dose, then titrate according to individual patient response
- Hypertension: Recommended initial dose is one tablet daily with food. If additional blood pressure reduction is needed, increase the dose.

CONTRAINDICATIONS: Anuria, Hypersensitivity

WARNINGS AND PRECAUTIONS:

Olmesartan:

- Avoid fetal (in utero) exposure
- Observe for signs and symptoms of hypotension in volume- or salt-depleted patients with treatment initiation
- Monitor for worsening renal function in patients with renal impairment

Chlortalidone:

- Hypotension: Higher risk for patients with impaired sympathetic response, volume-depletion or salt restriction.
- Renal Impairment: Patients with pre-existing kidney disease may be at higher risk.
- Monitor serum electrolytes periodically.

ADVERSE REACTIONS:
The most common side effect is dizziness. Other side effects include feeling tired, nausea, diarrhoea, headache, and decreased blood pressure.

DRUG INTERACTIONS

- Antihypertensive drugs: Chlortalidone may add to or potentiate the action of other antihypertensive drugs.
- Lithium: Lithium renal clearance is reduced by chlortalidone, increasing the risk of lithium toxicity.
- Olmesartan: NSAID use may lead to increased risk of renal impairment and loss of antihypertensive effect.

USE IN SPECIFIC POPULATIONS:

- **Pregnancy:** May cause fetal harm
- **Lactation:** Breastfeeding not recommended
- **Pediatrics:** Safety and efficacy in children have not been established
- **Geriatric Use:** No overall difference in responses versus younger patients but care should be taken in dose selection in patients with impaired renal function

PACKING: 3x10 ALU-ALU Pack

STORAGE: Store below 30°c. Protect from light and moisture.

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Bueno Salud Care India Pvt. Ltd.
Ahmedabad, Gujarat, India.

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