OLMECIP H Tablets (Olmesartan medoxomil + Hydrochlorothiazide)

Black Box Warning: Foetal Toxicity

• When pregnancy is detected, discontinue OLMECIP H as soon as possible (See WARNINGS AND PRECAUTIONS).
• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing foetus (See WARNINGS AND PRECAUTIONS).

Composition

OLMECIP H 20

Each film-coated tablet contains
Olmesartan medoxomil..................20 mg
Hydrochlorothiazide ....................12.5 mg

OLMECIP H 40

Each film-coated tablet contains
Olmesartan medoxomil.................40 mg
Hydrochlorothiazide.....................12.5 mg

Dosage Form

Tablets

Description

OLMECIP H is a combination of an angiotensin II receptor antagonist (AT₁ subtype), olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide.

Pharmacology

Pharmacodynamics

Olmesartan Medoxomil

Angiotensin II is formed from angiotensin I in a reaction catalysed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS), 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 AT\textsubscript{2} 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 AT\textsubscript{1} receptor than for the AT\textsubscript{2} receptor.

Blockade of the RAS 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 catalysed by ACE. Because olmesartan medoxomil does not inhibit ACE (kinase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance 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 (PRA) and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

Olmesartan medoxomil doses of 2.5 to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and PRA increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

**Hydrochlorothiazide**

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

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

**Pharmacokinetics**

**Absorption and Distribution**

**Olmesartan Medoxomil**

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. 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. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak
plasma concentration ($C_{\text{max}}$) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

The volume of distribution of olmesartan is approximately 17 L. 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 rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the foetus. Olmesartan was distributed to milk at low levels in rats.

**Hydrochlorothiazide**

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

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

**Metabolism and Excretion**

**Olmesartan Medoxomil**

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 faeces via the bile.

**Hydrochlorothiazide**

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

**Special Populations**

**Paediatric**

The pharmacokinetics of olmesartan as well as hydrochlorothiazide have not been investigated in patients <18 years of age.

**Geriatric**

The pharmacokinetics of olmesartan were studied in the elderly (≥ 65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest accumulation of olmesartan was observed in the elderly with repeated dosing; AUC$_{\text{ss}}$, was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CL$_{\text{R}}$.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive older people compared to young healthy volunteers.

**Gender**

Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and $C_{\text{max}}$ were 10-15% higher in women than in men.
Pharmacokinetic differences with the use of hydrochlorothiazide based on gender is not known.

**Renal Impairment**

In patients with renal insufficiency, serum concentrations of olmesartan were elevated 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). The pharmacokinetics of olmesartan in patients undergoing haemodialysis has not been studied.

The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

**Hepatic Impairment**

Increases in $AUC_{0-\infty}$ and $C_{\text{max}}$ for olmesartan were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

**Indications**

**OLMECIP H** is indicated for the treatment of hypertension.

This fixed dose combination is not indicated for initial therapy.

**Dosage and Administration**

**General Consideration**

The usual recommended starting dose of olmesartan medoxomil is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily. To minimise dose-independent side effects, it is usually appropriate to begin **OLMECIP H** only after a patient has failed to achieve the desired effect with monotherapy, such as olmesartan medoxomil or hydrochlorothiazide.

**Replacement Therapy**

**OLMECIP H** may be substituted for its titrated components (olmesartan medoxomil and hydrochlorothiazide).

**Dose Titration by Clinical Effect**

A patient whose blood pressure is inadequately controlled by olmesartan or hydrochlorothiazide alone may be switched to once daily **OLMECIP H**.

Dosing should be individualised. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

If blood pressure is not controlled by olmesartan alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily.
If a patient is taking hydrochlorothiazide, olmesartan medoxomil may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control. If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding olmesartan or switching to OLMECIP H as marked decreases in blood pressure may occur. Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding olmesartan. The antihypertensive effect of OLMECIP H is related to the dose of both components over the range of 10–40 mg for olmesartan medoxomil and 12.5–25 mg for hydrochlorothiazide. The maximum recommended dose of olmesartan medoxomil is 40 mg/day and that of hydrochlorothiazide is 25 mg/day. This means that dose should not exceed one tablet of OLMECIP H 40 and two tablets of OLMECIP H 20 per day.

No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40mL/min) or with moderate to marked hepatic dysfunction. For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), OLMECIP H should be initiated under close medical supervision and consideration should be given to use of a lower starting dose.

The side effects of OLMECIP H are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalaemia). Some dose-independent phenomena (e.g., pancreatitis) do occur with hydrochlorothiazide. Therapy with any combination of olmesartan medoxomil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

OLMECIP H may be administered with other antihypertensive agents.

Renal Impairment

The usual regimens of therapy with OLMECIP H may be followed provided the patient’s creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so OLMECIP H is not recommended.

Hepatic Impairment

No dosage adjustment is necessary with hepatic impairment.

Contraindications

- Patients who are hypersensitive to any component of this product
- Patients with anuria or hypersensitivity to other sulphonamide-derived drugs
- Co-administered with aliskiren in patients with diabetes
- Patients with refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia
- Severe renal impairment (creatinine clearance <30 mL/min)
- Severe hepatic impairment, cholestasis and biliary obstructive disorders
- Second and third trimester of pregnancy

Warnings and Precautions

General

Hypotension in Volume- or Salt-Depleted Patients
In patients with an activated RAS, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with **OLMECIP H** as with any ARB. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. When electrolyte and fluid imbalances have been corrected, therapy usually can be continued without difficulty. A transient hypotensive response is not a contraindication to further treatment.

**Sprue-like Enteropathy**

Severe, chronic diarrhoea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other aetiologies. Consider discontinuation of **OLMECIP H** in cases where no other aetiology is identified.

**Hypersensitivity Reaction**

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

**Systemic Lupus Erythematosus**

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

**Acute Myopia and Secondary Angle-Closure Glaucoma**

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

**Fluid or Electrolyte Imbalance**

In a double-blind clinical trial of various doses of olmesartan medoxomil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalaemia (serum potassium <3.4 mEq/L) was 2.1%; the incidence of hyperkalaemia (serum potassium >5.7 mEq/L) was 0.4%. In this trial, no patient discontinued due to increases or decreases in serum potassium.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatraemia, hypochloraemic alkalosis and hypokalaemia. Serum and urine electrolyte determinations are important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalaemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after
prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatraemia may occur in oedematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatraemia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesaemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

**Hyperuricaemia**

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

**Hyperglycaemia**

In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Hyperglycaemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

**Post-sympathectomy**

The antihypertensive effects of hydrochlorothiazide may be enhanced in the post-sympathectomy patient.

**Hyperlipidaemia**

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

**Other Conditions with Stimulation of the RAS**

In patients whose vascular tone and renal function depend predominantly on the activity of the RAS (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

**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 RAS.
**Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy**

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

**Primary Aldosteronism**

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the RAS. Therefore, the use of **OLMECIP H** is not recommended in such patients.

**Antidoping Test**

Hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

**Other**

In general arteriosclerosis, in patients with ischaemic heart disease or ischaemic cerebrovascular disease, there is always a risk that excessive blood pressure decrease could result in a myocardial infarction or stroke.

**Drug Interactions**

**Olmesartan Medoxomil-Hydrochlorothiazide Combination**

**Lithium**

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of olmesartan or thiazide diuretics. Lithium levels should be monitored in patients receiving **OLMECIP H** and lithium.

**Non-Steroidal Anti-Inflammatory Agents (NSAIDs) 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 olmesartan medoxomil, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored periodically in patients receiving olmesartan medoxomil and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including olmesartan medoxomil may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients the administration of an NSAID can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when **OLMECIP H** and non-steroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

**Alcohol, Barbiturates, or Narcotics**

Concomitant administration may potentiate orthostatic hypotension.
**Other Antihypertensive Drugs**

Administration with other antihypertensives may cause additive effect or potentiation.

**Baclofen**

Potentiation of antihypertensive effect may occur.

**Amifostine**

Potentiation of antihypertensive effect may occur.

**Olmesartan Medoxomil**

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with hydrochlorothiazide, digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids containing aluminium hydroxide and magnesium hydroxide. Olmesartan medoxomil is not metabolised by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolised by those enzymes are not expected.

**Dual Blockade of the RAS**

Dual blockade of the RAS with angiotensin receptor blockers (ARBs), ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, combined use of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes should be closely monitored in patients on **OLMECIP H** and other agents that affect the RAS. Aliskiren should not be co-administered with **OLMECIP H** in patients with diabetes. Use of aliskiren with **OLMECIP H** should be avoided in patients with renal impairment [glomerular filtration rate (GFR) <60 mL/min].

**Colesevelam Hydrochloride**

Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administration of **OLMECIP H** at least 4 hours before the colesevelam hydrochloride dose should be considered.

**Medicinal Products Affecting Potassium Levels**

Based on experience with the use of other medicinal products that affect the RAS, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE inhibitors) may lead to increases in serum potassium. If medicinal products which affect potassium levels are to be prescribed in combination with **OLMECIP H**, monitoring of potassium plasma levels is advised.

**Hydrochlorothiazide**

**Antidiabetic Drugs (oral agents and insulin)**
Dosage adjustment of the antidiabetic drug may be required when administered concomitantly.

**Metformin**

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

**Cholestyramine and Colestipol Resins**

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

**Corticosteroids, Adrenocorticotropic Hormone (ACTH)**

Concomitant administration intensified electrolyte depletion, particularly hypokalaemia.

**Pressor Amines (E.g. Norepinephrine)**

Concomitant administration may possibly decrease response to pressor amines but not sufficient to preclude their use.

**Skeletal Muscle Relaxants, Non-depolarizing (E.g. Tubocurarine)**

Possible increased responsiveness to the muscle relaxant is expected on concomitant administration.

**Medicinal Products Affecting Potassium Levels**

The potassium depleting effect of hydrochlorothiazide may be potentiated by the coadministration of other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended.

**Calcium Salts**

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

**Digitalis Glycosides**

Thiazide induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis induced cardiac arrhythmias.

**Anticholinergic Agents (e.g. Atropine, Biperiden)**

Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

**Beta-blockers and Diazoxide**

The hyperglycaemic effect of beta blockers and diazoxide may be enhanced by thiazides.

**Cytotoxic Agents (E.g. Cyclophosphamide, Methotrexate)**
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

**Renal Impairment**

As a consequence of inhibiting the RAS, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the RAS (e.g. patients with severe congestive heart failure), treatment with ACE inhibitors and ARBs has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

**OLMECIP H** should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance is ≥30 mL/min, <60 mL/min). However, in such patients **OLMECIP H** should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. If progressive renal impairment becomes evident, withholding or discontinuing **OLMECIP H** should be considered. In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function.

**Hepatic Impairment**

No dosage adjustment is necessary in patients with hepatic impairment. However, **OLMECIP H** should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance due to thiazides may precipitate hepatic coma.

**Pregnancy**

**Category D**

Use of drugs that act on the RAS during the second and third trimesters of pregnancy reduces foetal renal function and increases foetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with foetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected **OLMECIP H** should be discontinued as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining foetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the RAS from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimise outcomes for both mother and foetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the RAS for a particular patient, apprise the mother of the potential risk to the foetus. Serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, **OLMECIP H** should be discontinued, unless it is considered lifesaving for the mother.
Foetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury. Infants with histories of in-utero exposure to olmesartan medoxomil-hydrochlorothiazide combination for hypotension, oliguria, and hyperkalaemia should be closely observed.

There is no clinical experience with the use of olmesartan medoxomil-hydrochlorothiazide in pregnant women. Preclinical studies demonstrated no teratogenic effects when the combination of olmesartan medoxomil and hydrochlorothiazide in the ratio of 1.6:1 was administered to pregnant mice at oral doses up to 1625 mg/kg/day (122 times the maximum recommended human dose [MRHD] on a mg/m² basis) or pregnant rats at oral doses up to 1625 mg/kg/day (280 times the MRHD on a mg/m² basis). In rats, however, foetal 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, 162.5 mg/kg/day, is about 28 times, on an mg/m² basis, the MRHD of 40 mg olmesartan medoxomil with 25 mg hydrochlorothiazide per day.

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

**Lactation**

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration 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.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue **OLMECIP H**, taking into account the importance of the drug to the mother.

**Paediatric Use**

*Neonates with a History of in Utero Exposure to Olmesartan medoxomil-Hydrochlorothiazide Combination*

If oliguria or hypotension 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.

Safety and effectiveness in paediatric patients have not been established.

**Geriatric Use**

Clinical studies of olmesartan-hydrochlorothiazide combination did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.
Undesirable Effects

Clinical Trials

Olmesartan Medoxomil-Hydrochlorothiazide Combination

Olmesartan medoxomil-hydrochlorothiazide has been evaluated for safety in 1243 hypertensive patients. Treatment with olmesartan medoxomil-hydrochlorothiazide combination was well tolerated, with an incidence of adverse events similar to placebo. Events generally observed are mild, transient and had no relationship to the dose of olmesartan medoxomil-hydrochlorothiazide combination.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil-hydrochlorothiazide and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% (25/1243) of patients treated with olmesartan medoxomil-hydrochlorothiazide and 2.0% (7/342) of patients treated with placebo.

In a placebo-controlled clinical trial, the following adverse events reported with olmesartan medoxomil-hydrochlorothiazide occurred in >2% of patients, and more often on the olmesartan medoxomil-hydrochlorothiazide combination than on placebo, regardless of drug relationship (Table)

Table: Adverse events reported in the study groups

<table>
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<th>Olmesartan/HCTZ (N=247) (%)</th>
<th>Placebo (N=42) (%)</th>
<th>Olmesartan (N=125) (%)</th>
<th>HCTZ (N=88) (%)</th>
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<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Hyperuricaemia</td>
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<td><strong>Nervous system</strong></td>
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<td>Dizziness</td>
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<td>1</td>
<td>8</td>
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<tr>
<td><strong>Respiratory</strong></td>
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<td></td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>7</td>
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</table>

The following adverse events were also reported at a rate of >2%, but were as, or more, common in the placebo group: headache and urinary tract infection.

Other adverse events that have been reported with an incidence of greater than 1.0%, whether or not attributed to treatment, in the more than 1200 hypertensive patients treated with olmesartan medoxomil-hydrochlorothiazide in controlled or open-label trials are listed below.

**Body as a Whole**: Chest pain, back pain, peripheral oedema

**Central and Peripheral Nervous System**: Vertigo

**Gastrointestinal**: abdominal pain, dyspepsia, gastroenteritis, diarrhoea

**Liver and Biliary System**: SGOT increased, GGT increased, SGPT increased

**Metabolic and Nutritional**: Hyperlipaemia, creatine phosphokinase increased, hyperglycaemia
Musculoskeletal: Arthritis, arthralgia, myalgia

Respiratory System: Coughing

Skin and Appendages Disorders: Rash

Urinary System: Haematuria

Facial oedema was reported in 2/1243 patients receiving olmesartan medoxomil-hydrochlorothiazide. Angioedema has been reported with angiotensin II receptor antagonists.

Olmesartan Medoxomil

Other adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are tachycardia and hypercholesterolaemia.

Hydrochlorothiazide

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

Body as a Whole: Weakness

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

Haematologic: Aplastic anaemia, agranulocytosis, leukopenia, haemolytic anaemia, thrombocytopenia

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

Metabolic: Hyperglycaemia, glycosuria, hyperuricaemia

Musculoskeletal: Muscle spasm

Nervous System/Psychiatric: Restlessness

Renal: Renal failure, renal dysfunction, interstitial nephritis

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

Special Senses: Transient blurred vision, xanopsia

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil-hydrochlorothiazide.

Creatinine, Blood Urea Nitrogen: Increases in blood urea nitrogen (BUN) and serum creatinine of
>50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil-hydrochlorothiazide due to increased BUN or creatinine.

**Haemoglobin and Haematocrit:** A greater than 20% decrease in haemoglobin and haematocrit was observed in 0.0% and 0.4% (one patient), respectively, of olmesartan medoxomil-hydrochlorothiazide patients, compared with 0.0% and 0.0%, respectively, in placebo-treated patients. No patients were discontinued due to anaemia.

**Post-Marketing Experience**

The following adverse reactions have been reported in post-marketing experience:

**Body as a Whole:** Asthenia, angio-oedema, anaphylactic reactions, peripheral oedema

**Gastrointestinal:** Vomiting, diarrhoea, sprue-like enteropathy

**Metabolic and Nutritional Disorders:** Hyperkalaemia

**Musculoskeletal:** Rhabdomyolysis

**Urogenital System:** Acute renal failure, increased blood creatinine levels

**Skin and Appendages:** Alopecia, pruritus, urticarial

Data from one controlled trial and an epidemiologic study have suggested that high-dose olmesartan may increase cardiovascular (CV) risk in diabetic patients, but the overall data are not conclusive. The randomized, placebo-controlled, double-blind ROADMAP trial (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention trial, n=4447) examined the use of olmesartan, 40 mg daily, vs. placebo in patients with type 2 diabetes mellitus, normoalbuminuria, and at least one additional risk factor for CV disease. The trial met its primary endpoint, delayed onset of microalbuminuria, but olmesartan had no beneficial effect on decline in GFR. There was a finding of increased CV mortality (adjudicated sudden cardiac death, fatal myocardial infarction, fatal stroke, revascularization death) in the olmesartan group compared to the placebo group (15 olmesartan vs. 3 placebo, hazard ration [HR] 4.9, 95% confidence interval [CI], 1.4, 17), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

The epidemiologic study included patients 65 years and older with overall exposure of > 300,000 patient-years. In the sub-group of diabetes patients receiving high-dose olmesartan (40 mg/d) for > 6 months, there appeared to be an increased risk of death (HR 2.0, 95% CI 1.1, 3.8) compared to similar patients taking ARBs. In contrast, high-dose olmesartan use in non-diabetic patients appeared to be associated with a decreased risk of death (HR 0.46, 95% CI 0.24, 0.86) compared to similar patients taking other ARBs. No differences were observed between the groups receiving lower doses of olmesartan compared to other angiotensin blockers or those receiving therapy for <6 months.

Overall, these data raise a concern of a possible increased CV risk associated with the use of high-dose olmesartan in diabetic patients. There are, however, concerns with the credibility of the finding of increased CV risk, notably the observation in the large epidemiologic study for a survival benefit in non-diabetics of a magnitude similar to the adverse finding in diabetics. Importantly, the safety review done by the U.S. Food and Drug Administration (FDA) has found no clear evidence of increased cardiovascular risks associated with use of the olmesartan in diabetes patients.
Others

Other adverse reactions of hydrochlorothiazide and olmesartan medoxomil combination in clinical trials, post-authorisation safety studies and spontaneous reporting as well as adverse reactions from the individual components olmesartan medoxomil and hydrochlorothiazide based on the known safety profile of these substances are summarised below. Terminologies used in order to classify the occurrence of the following adverse reactions: common (≥1/100); uncommon (≥1/1,000 to <1/100) and rare (<1/1,000)

**Olmesartan Medoxomil-Hydrochlorothiazide Combination**

*Common*: Chest pain. Fatigue

*Uncommon*: Hypertriglyceridaemia, somnolence, syncope, palpitations, hypotension, orthostatic hypotension, vomiting, eczema, back pain, pain in extremity, erectile dysfunction, alanine aminotransferase increased, aspartate aminotransferase increased, blood calcium increased, gamma glutamyl transferase increased

*Rare*: Disturbance in consciousness (such as loss of consciousness), angioneurotic oedema, urticarial, malaise, blood haematocrit decreased, blood haemoglobin decreased, blood urea nitrogen increased

**Olmesartan Medoxomil**

*Common*: Hypertriglyceridaemia, bronchitis, pharyngitis, rhinitis, back pain, skeletal pain, chest pain, fatigue, influenza-like symptoms, pain

*Uncommon*: Angina pectoris, vomiting, exanthema, urticarial, face oedema, malaise

*Rare*: Hypotension, angioneurotic oedema, renal insufficiency, lethargy

**Hydrochlorothiazide**

*Common*: Glykosuria, hypercalcaemia, hypertriglyceridaemia, hypochloraemia, hypokalaemia, hyponatriaemia, hypermylasaemia, confusion, constipation, meteorism, vomiting

*Uncommon*: Anorexia, loss of appetite, worsening of pre-existing myopia, orthostatic hypotension, dyspnoea, photosensitivity reactions, purpura, urticarial, erectile dysfunction

*Rare*: Bone marrow depression, neutropenia / agranulocytosis, apathy, depression, sleep disturbances, convulsions, paraesthesia, lacrimation decreased, cardiac arrhythmias, embolism, necrotising angiitis (vasculitis, cutaemous vasculitis), thrombosis, acute cholecystitis, cutaneous lupus erythematodes-like reactions, reactivation of cutaemous lupus erythematoses, muscular weakness, paresis

**Overdosage**

**Olmesartan Medoxomil**

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialysability of olmesartan is unknown.
No lethality was observed in acute toxicity studies in mice and rats given single oral doses up to 2000 mg/kg olmesartan medoxomil. The minimum lethal oral dose of olmesartan medoxomil in dogs was greater than 1500 mg/kg.

**Hydrochlorothiazide**

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established. The oral median lethal dose (LD$_{50}$) of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

**Incompatibility**

Not applicable

**Shelf-Life**

2 years

**Storage & Handling Instructions**

Store in a cool dry place. Protect from light.

**Packaging Information**

**OLMECIP H 20:** Blister pack of 10 tablets  
**OLMECIP H 40:** Blister pack of 10 tablets

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