PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr TEVA-OLMESARTAN / HCTZ

Olmesartan Medoxomil and Hydrochlorothiazide Tablets

Tablets, 20 mg / 12.5 mg, 40 mg / 12.5 mg, and 40 mg / 25 mg, Oral

Angiotensin II $AT_1$ Receptor Blocker – Diuretic

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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 2 CONTRAINDICATIONS, Pregnancy and Breastfeeding | December 2021 |
| 7 WARNINGS AND PRECAUTIONS, 7.1.1 Special Populations, Pregnant Women | December 2021 |
| 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis, Non-melanoma Skin-Cancer | December 2021 |
| 7 WARNING AND PRECAUTIONS, Sensitivity/Resistance, Photosensitivity | December 2021 |

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

TEVA-OLMESARTAN / HCTZ (Olmesartan Medoxomil and Hydrochlorothiazide Tablets) is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

TEVA-OLMESARTAN / HCTZ is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**).

#### 1.1 Pediatrics

**Pediatrics (<18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (≥65 years of age):** Reported clinical experience has not identified differences in responses between elderly and younger patients, however, greater sensitivity of some older individuals cannot be ruled out (see **DOSAGE AND ADMINISTRATION**).

### 2 CONTRAINDICATIONS

- TEVA-OLMESARTAN / HCTZ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**
- Because of the hydrochlorothiazide component, TEVA-OLMESARTAN / HCTZ is contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.
- Concomitant use of angiotensin receptor antagonists (ARBs) -including the "*olmesartan medoxomil*" component of TEVA-OLMESARTAN / HCTZ, with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 ml/min/1.73 $m^2$) is contraindicated (see **WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs**).
- Pregnant women (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**)
- Breast-feeding women (see WARNINGS AND PRECAUTIONS, Special Populations, Breastfeeding)

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

When used in pregnancy, angiotensin receptor ($AT_1$) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, TEVA-OLMESARTAN / HCTZ should be discontinued as soon as possible (see **WARNINGS AND PRECAUTIONS, Special Populations**).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

- TEVA-OLMESARTAN / HCTZ is not for initial therapy.
- The dosage must be individualized.
- To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.
- The dose of TEVA-OLMESARTAN / HCTZ should be determined by the titration of the individual components.

### 4.2 Recommended Dose and Dosage Adjustment

**Replacement Therapy**

Once the patient has been stabilized on the individual components as described below, TEVA-OLMESARTAN / HCTZ may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination.

**Dose Titration by Clinical Effect**

TEVA-OLMESARTAN / HCTZ is available in strengths of 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg. A patient whose blood pressure is inadequately controlled by olmesartan medoxomil or hydrochlorothiazide alone may be switched to once daily TEVA-OLMESARTAN / HCTZ. Dosage should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

The antihypertensive effect of TEVA-OLMESARTAN / HCTZ is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see **ACTION AND CLINICAL PHARMACOLOGY**). The dose of TEVA-OLMESARTAN / HCTZ is one tablet once daily. More than one tablet daily is not recommended.

**Elderly:** No adjustment of dose is generally required in elderly patients (see below for dose recommendation in patients with renal impairment). If up-titration to the maximum dose of 40 mg/25 mg daily is required, blood pressure should be closely monitored (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

**Hepatic Impairment:** No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore, a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil- hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of olmesartan is eliminated in the bile.

No information is available in patients with severe liver disease; therefore, use of TEVA-OLMESARTAN / HCTZ in this group of patients is not recommended (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

**Renal Impairment:** Owing to the limited experience of higher dosages in this patient group, the maximum dose in patients with mild to moderate renal impairment is 20 mg/12.5 mg once daily. The use of olmesartan medoxomil in patients with severe renal impairment is not recommended, since there is only limited experience in this patient group. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so TEVA-OLMESARTAN / HCTZ is not recommended.

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), TEVA-OLMESARTAN / HCTZ should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see WARNINGS AND PRECAUTIONS, Renal).

The side effects (see **WARNINGS AND PRECAUTIONS**) of olmesartan medoxomil are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalemia). 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. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

**Olmesartan Medoxomil Monotherapy**
The usual recommended starting dose of olmesartan medoxomil monotherapy is 20 mg once daily 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. Twice-daily dosing offers no advantage over the same total dose given once daily.

- **Elderly:** No adjustment of dose is generally required in elderly patients (see below for dose recommendation in patients with renal impairment). If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

- **Hepatic Impairment:** No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore, a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil-hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of olmesartan is eliminated in the bile. No information is available in patients with severe liver disease; therefore, use of olmesartan medoxomil in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

- **Renal Impairment:** Owing to the limited experience of higher dosages in this patient group, the maximum dose in patients with mild to moderate renal impairment is 20 mg olmesartan medoxomil once daily. The use of olmesartan medoxomil in patients with severe renal

impairment is not recommended, since there is only limited experience in this patient group.

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), TEVA-OLMESARTAN / HCTZ should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS AND PRECAUTIONS, Renal**).

If blood pressure is not controlled by olmesartan medoxomil alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily.

**Hydrochlorothiazide**:
Effective in doses between 12.5 mg and 50 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 medoxomil or switching to TEVA-OLMESARTAN / HCTZ as marked decreases in blood pressure may occur (see WARNINGS AND PRECAUTIONS, Renal). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding olmesartan medoxomil.

### 4.3 Reconstitution
Not applicable

### 4.4 Administration
TEVA-OLMESARTAN / HCTZ may be administered with or without food.

### 4.5 Missed Dose
If patients miss a dose, they should wait until their next scheduled dose. Patients should not double their dose.

## 5 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 dialyzability of olmesartan is unknown.

**Hydrochlorothiazide**
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. **Treatment should be symptomatic and supportive.**

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| For management of a suspected drug overdose, contact your regional poison control centre. |

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength / Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablet / 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg | hydroxypropylcellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sunset yellow FCF aluminum lake (20 mg/12.5 mg and 40 mg/12.5 mg only), titanium dioxide, triacetin, and yellow iron oxide |

COMPOSITION: TEVA-OLMESARTAN / HCTZ is supplied as:

**20 mg/12.5 mg**: Orange, round, biconvex, film-coated tablets with “OH 21” debossed on one face and plain on the other side.

**40 mg/12.5 mg**: Orange, oval, biconvex, film-coated tablets with “OH 41” debossed on one face and plain on the other side.

**40 mg/25 mg**: Pink, oval, biconvex film-coated tablets with “OH 42” debossed on one face and plain on the other side.

PACKAGING:
20 mg/12.5 mg, 40 mg/12.5 mg, and 40 mg/25 mg tablets: Blister packs, i.e. blister strips of 10 tablets (3 strips/carton) and bottles of 100 tablets.

## 7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

**Carcinogenesis and Mutagenesis**
**Non-melanoma skin cancer:** An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see **NON-CLINICAL TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide**).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

**Cardiovascular**

**Hypotension in Volume- or Salt-Depleted Patients:** In patients with an activated renin-angiotensin system, 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 TEVA-OLMESARTAN / HCTZ. Treatment should start under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see **DOSAGE AND ADMINISTRATION**). 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.

- **Valvular Stenosis:** there is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.

**Dual blockade of the Renin-Angiotensin System (RAS)**

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as the "*olmesartan medoxomil*" component of TEVA-OLMESARTAN / HCTZ, or of angiotensin-converting-enzyme inhibitors (ACE inhibitors) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73 $m^2$). Therefore, the use of TEVA-OLMESARTAN / HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see **CONTRAINDICATIONS**). Further, co-administration of ARBs, including the "*olmesartan medoxomil*" component of TEVA-OLMESARTAN / HCTZ, with other agents blocking the RAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure and hyperkalemia.

**Endocrine and Metabolism**

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis and hypokalemia. Serum and urine electrolyte determinations are 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.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or

after prolonged therapy.
TEVA-OLMESARTAN / HCTZ contains olmesartan, a drug that inhibits the renin-angiotensin system (RAS). Drugs that inhibit the RAS can cause hyperkalaemia. Monitor serum electrolytes periodically.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia 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 during thiazide therapy 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 hyponatremia may occur in edematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia 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 hypomagnesemia.

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

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides may decrease PBI levels without signs of thyroid disturbance.

Hyperglycemia may occur with thiazide diuretics. Insulin or oral hypoglycemic agents requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy.

**Gastrointestinal**

**Sprue-like Enteropathy**: Severe, chronic diarrhea 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 and no other etiology is identified, discontinue TEVA-OLMESARTAN / HCTZ.

**Hepatic/Biliary/Pancreatic**

No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil-hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary

obstructive disorders, as the majority of olmesartan is eliminated in the bile. No information is available in patients with severe liver disease; therefore, use of olmesartan medoxomil in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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

**Ophthalmologic**

**Acute Myopia and Secondary Angle-Closure Glaucoma:** Hydrochlorothiazide, a sulfonamide, 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 sulfonamide or penicillin allergy.

**Renal**

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, 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 renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely, acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

The use of ARBs – including the "*olmesartan medoxomil*" component of TEVA-OLMESARTAN / HCTZ, or ACE inhibitors with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR< 60 ml/min/1.73m$^2$) (See **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs**).

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.

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

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

**Sensitivity/Resistance**

**Hypersensitivity:** Anaphylactic reactions have been reported very rarely in patients treated with olmesartan.

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.

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

**Photosensitivity:** Photosensitivity reactions have been reported with the use of thiazide diuretics. If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

Drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, TEVA-OLMESARTAN / HCTZ should be discontinued as soon as possible. If TEVA-OLMESARTAN / HCTZ is used during pregnancy, or if the patient becomes pregnant while taking TEVA-OLMESARTAN / HCTZ, the patient should be apprised of the potential hazard to a fetus.

The use of ARBs is contraindicated during pregnancy. 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.

The use of ARBs 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, hyperkalemia). Should exposure to TEVA-OLMESARTAN / HCTZ have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended.

Infants with a history of in utero exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

Animal Data

No teratogenic effects were observed when 1.6:1 combinations of olmesartan medoxomil and

hydrochlorothiazide were administered to pregnant mice at oral doses up to 1625 mg/kg/day (122 times the maximum recommended human dose [MRHD] on a mg/ $m^2$ basis) or pregnant rats at oral doses up to 1625 mg/kg/day (280 times the MRHD on a mg/ $m^2$ basis). In rats, however, fetal body weights at 1625 mg/kg/day (a toxic, sometimes lethal dose in the dams) were significantly lower than control. The no observed effect dose for developmental toxicity in rats,162.5 mg/kg/day, is about 28 times, on a mg/$m^2$ basis, the MRHD of olmesartan medoxomil and hydrochlorothiazide (40 mg olmesartan medoxomil/25 mg hydrochlorothiazide/day).

### 7.1.2 Breast-feeding

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

### 7.1.3 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics (≥65 years of age)

Reported clinical experience has not identified differences in responses between elderly and younger patients, however, greater sensitivity of some older individuals cannot be ruled out (see **CLINICAL TRIALS**).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

*Olmesartan medoxomil-hydrochlorothiazide*

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

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 discontinuations 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. The following potentially serious adverse reactions have been reported with olmesartan medoxomil / olmesartan medoxomil-hydrochlorothiazide in controlled trials: syncope, hypotension.

### 8.2 Clinical Trial Adverse Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be*

*compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

In a placebo-controlled clinical trial, the following adverse events were reported with olmesartan medoxomil-hydrochlorothiazide in >1% of patients (Table 1).

**Table 1: Adverse Events[a] Occurring >1% in Placebo-controlled Cohort**

| | **Total Placebo ALONE** (N = 42) | **Total HCTZ ALONE** (N = 88) | **Total Olmesartan Medoxomil ALONE** (N = 125) | **Total Olmesartan Medoxomil + HCTZ** (N = 247) |
|---|---|---|---|---|
| **System Organ Class (SOC)** | | | | |
| **MedDRA Preferred Term** | N (%) | N (%) | N (%) | N (%) |
| **Ear and labyrinth disorders** | | | | |
| Ear disorder | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (2.0%) |
| **Gastrointestinal disorders** | | | | |
| Nausea | 0 (0.0%) | 1 (1.1%) | 2 (1.6%) | 7 (2.8%) |
| Abdominal pain | 1 (2.4%) | 1 (1.1%) | 4 (3.2%) | 5 (2.0%) |
| Dyspepsia | 0 (0.0%) | 4 (4.5%) | 2 (1.6%) | 5 (2.0%) |
| Diarrhea | 1 (2.4%) | 2 (2.3%) | 4 (3.2%) | 4 (1.6%) |
| Gastroenteritis | 1 (2.4%) | 0 (0.0%) | 0 (0.0%) | 3 (1.2%) |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 0 (0.0%) | 1 (1.1%) | 3 (2.4%) | 5 (2.0%) |
| Influenza like illness | 0 (0.0%) | 1 (1.1%) | 1 (0.8%) | 3 (1.2%) |
| **Immune system disorders** | | | | |
| Hypersensitivity | 0 (0.0%) | 1 (1.1%) | 1 (0.8%) | 3 (1.2%) |
| **Infections and Infestations** | | | | |
| Upper respiratory tract infection | 0 (0.0%) | 6 (6.8%) | 8 (6.4%) | 16 (6.5%) |
| Urinary tract infections | 1 (2.4%) | 1 (1.1%) | 1 (0.8%) | 8 (3.2%) |
| Pharyngitis | 0 (0.0%) | 1 (1.1%) | 1 (0.8%) | 4 (1.6%) |
| Rhinitis | 2 (4.8%) | 0 (0.0%) | 3 (2.4%) | 4 (1.6%) |
| Sinusitis | 1 (2.4%) | 2 (2.3%) | 3 (2.4%) | 3 (1.2%) |
| **Injury, poisoning and procedural complications** | | | | |
| Injury | 0 (0.0%) | 3 (3.4%) | 1 (0.8%) | 6 (2.4%) |
| **Metabolism and nutrition disorders** | | | | |
| Hyperuricemia | 1 (2.4%) | 2 (2.3%) | 0 (0.0%) | 10 (4.0%) |
| Hyperglycemia | 1 (2.4%) | 2 (2.3%) | 0 (0.0%) | 5 (2.0%) |

**Table 1: Adverse Events[a] Occurring >1% in Placebo-controlled Cohort**

| | **Total Placebo ALONE** | **Total HCTZ ALONE** | **Total Olmesartan Medoxomil ALONE** | **Total Olmesartan Medoxomil + HCTZ** |
|---|---|---|---|---|
| | (N = 42) | (N = 88) | (N = 125) | (N = 247) |
| **System Organ Class (SOC)** | | | | |
| **MedDRA Preferred Term** | N (%) | N (%) | N (%) | N (%) |
| Hyperlipemia | 0 (0.0%) | 1 (1.1%) | 1 (0.8%) | 4 (1.6%) |
| BUN increased | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (1.6%) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Back pain | 1 (2.4%) | 2 (2.3%) | 3 (2.4%) | 5 (2.0%) |
| Myalgia | 0 (0.0%) | 1 (1.1%) | 4 (3.2%) | 5 (2.0%) |
| **Nervous system disorders** | | | | |
| Dizziness | 1 (2.4%) | 7 (8.0%) | 1 (0.8%) | 23 (9.3%) |
| Headache | 3 (7.1%) | 4 (4.5%) | 11 (8.8%) | 13 (5.3%) |
| **Renal and urinary disorders** | | | | |
| Hematuria | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 6 (2.4%) |
| Pyuria | 0 (0.0%) | 1 (1.1%) | 1 (0.8%) | 4 (1.6%) |
| Urine analysis abnormal | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (1.6%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 0 (0.0%) | 0 (0.0%) | 2 (1.6%) | 5 (2.0%) |
| **Vascular disorders** | | | | |
| Hypotension | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (1.2%) |

[a] Adverse events reported in >1% of patients in the Total Olmesartan Medoxomil + HCTZ treatment group.

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.

Gastrointestinal disorders: abdominal pain, dyspepsia, diarrhea.
General disorders and administration site conditions: chest pain, edema peripheral.
Infections and infestations: gastroenteritis.
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, creatine phosphokinase increased, gamma-glutamyltransferase increased.
Musculoskeletal and connective tissue disorders: arthritis, arthralgia, back pain, myalgia.
Nervous system disorders: vertigo.
Renal and urinary disorders: hematuria.
Respiratory, thoracic and mediastinal disorders: cough.

Skin and subcutaneous tissue disorders: rash.

### 8.3 Less Common Clinical Trial Adverse Reactions (<1%)

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

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

*Liver Functions Tests:* elevations of liver enzymes and/or serum bilirubin were observed infrequently.

| | Placebo | HCTZ | Olmesartan Medoxomil | Olmesartan Medoxomil + HCTZ |
|---|---|---|---|---|
| | (n=42) | N=88) | (n=125) | (n=247) |
| CPK increased | 2 (4.8%) | 2 (2.3%) | 3 (2.4%) | 4 (1.6%) |
| γGT increased | 1 (2.4%) | 1 (1.1%) | 3 (2.4%) | 3 (1.2%) |
| ALT increased | 2 (4.8%) | 1 (1.1%) | 3 (2.4%) | 3 (1.2%) |
| AST increased | 1 (2.4%) | 1 (1.1%) | 3 (2.4%) | 3 (1.2%) |

*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.

*Hemoglobin and Hematocrit:* A greater than 20% decrease in hemoglobin and hematocrit 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 anemia.

### 8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable

### 8.6 Post-Market Adverse Reactions

Other adverse events reported rarely in post-marketing use include: asthenia, angioedema, vomiting, hyperkalemia, rhabdomyolysis, renal failure acute, blood creatinine increased, alopecia, pruritus, urticaria, palpitations, syncope, blood uric acid increased and sprue-like enteropathy.

Anaphylactic reactions have been reported very rarely in patients treated with olmesartan.

In the Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study including 4447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, 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 (0.67%) vs. 3 patients

(0.14%) (HR=4.94; 95% CI=1.43-17.06)). The patient population at increased risk had preexisting coronary artery disease.

**Non-melanoma skin cancer**
Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested that, with important uncertainty, the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions Box
Not applicable

### 9.2 Overview
Not applicable

### 9.3 Drug-Drug Interactions
The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated.

**Olmesartan medoxomil**

Table 2 Established or Potential Drug-Drug Interactions with Olmesartan medoxomil

| Common name | Ref. | Effect | Clinical comment |
|---|---|---|---|
| Antacids | CT | The bioavailability of olmesartan was not significantly altered when co-administered with antacids [$Al(OH)_3/Mg(OH)_2$] | |
| Cytochrome P450 Enzyme System | T | Unlike some other angiotensin II receptor blockers, olmesartan medoxomil is not metabolized by cytochrome P450 enzymes. Interactions with drugs that inhibit, | |

| | | | |
|---|---|---|---|
| | | induce or are metabolized by these enzymes are not expected. | |
| Digoxin | CT | No pharmacokinetics or pharmacodynamics effects were reported when olmesartan medoxomil was co-administered with digoxin in healthy volunteers. | |
| Diuretics | CT | Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction in blood pressure after initiation of therapy with olmesartan. | The possibility of symptomatic hypotension with the use of olmesartan can be minimized by discontinuing the diuretic prior to initiation of treatment (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension in Volume- or Salt-Depleted Patients**). No drug interaction of clinical significance has been identified with thiazide diuretics. |
| Dual blockage of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs | T | Co-administration of angiotensin receptor antagonists (ARBs), such as the "*olmesartan medoxomil*" component of TEVA-OLMESARTAN / HCTZ, or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73 $m^2$). | Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure and hyperkalemia (See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)**). |
| Lithium Salts | T | As with other drugs which eliminate | Serum lithium levels should be |

| | | | |
|---|---|---|---|
| | | sodium, lithium clearance may be reduced in the presence of olmesartan. | monitored carefully if lithium salts are to be administered with olmesartan medoxomil. |
| Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors) | T | 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, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.<br><br>The administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. | Renal function should be monitored periodically in patients receiving olmesartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including olmesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.<br><br>When TEVA-OLMESARTAN / HCTZ and NSAID agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained. |
| *Warfarin* | CT | There was no effect on either the pharmacokinetics or pharmacodynamics of warfarin when co-administered with olmesartan medoxomil in healthy volunteers. | |

**Hydrochlorothiazide**
When administered concurrently the following drugs may interact with thiazide diuretics:

Table 3 Established or Potential Drug-Drug Interactions with Hydrochlorothiazide

| Proper Name | Ref. | Effect | Clinical comment |
|---|---|---|---|
| Agents Increasing Serum Potassium | T | Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increase in serum potassium. | Since olmesartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium when olmesartan medoxomil therapy is initiated. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that olmesartan may have on serum potassium. |
| Alcohol, barbiturates, or narcotics | C | Potentiation of orthostatic hypotension may occur. | Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy. |
| Amphotericin B | T | Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics. | Monitor serum potassium level. |
| Antidiabetic agents (e.g. insulin and oral hypoglycemic agents) | CT | Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance. | Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required. |
| Antihypertensive drugs | CT | Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, betablockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors). | |
| Antineoplastic drugs, including cyclophosphamide and methotrexate | C | Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. | Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required. |
| Bile acid sequestrants, eg. cholestyramine | CT | Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%.<br>Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothaizide by 30-35%. | Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary. |

| Proper Name | Ref. | Effect | Clinical comment |
|---|---|---|---|
| Calcium and vitamin D supplements | C | Thiazides decrease renal excretion of calcium and increase calcium release from bone. | Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary. |
| Carbamazepine | C | Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia. | Monitor serum sodium levels. Use with caution. |
| Corticosteroids, and adrenocorticotropic hormone (ACTH) | T | Intensified electrolyte depletion, particularly hypokalemia, may occur. | Monitor serum potassium, and adjust medications, as required. |
| Digoxin | CT | Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events. | Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required. |
| Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone | CT, T | Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics. | Dose adjustment of thiazide may be required. |
| Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors) | T, RC | Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol. | Dosage adjustment of gout medications may be required. |
| Lithium | CT | Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity. | Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely. |
| Nonsteroidal anti-inflammatory drugs (NSAID) | CT | NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of | If combination use is necessary, monitor renal function, serum potassium, |

| Proper Name | Ref. | Effect | Clinical comment |
|---|---|---|---|
| | | thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk. | and blood pressure closely. Dose adjustments may be required. |
| Pressor Amines (e.g., Norepinephrine) | T | In the presence of diuretics, possible decreased response to pressor amines may occur but the effect is not sufficient to preclude their use. | |
| Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline) | T, C | Concomitant use with thiazide diuretics may potentiate hyponatremia. | Monitor serum sodium levels. Use with caution. |
| Skeletal muscle relaxants of the curare family, eg., tubocurare | C | Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives. | |
| Topiramate | CT | Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations. | Monitor serum potassium and topiramate levels. Use potassium supplements, or concentrations. Adjust topiramate dose as necessary. |

C=Case Study; RCS=Retrospective Cohort Study; CT=Clinical Trial; T=Theoretical

### 9.4 Drug-Food Interactions

TEVA-OLMESARTAN / HCTZ may be administered with or without food.

### 9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

### 9.7 Drug-Lifestyle Interactions

Not applicable

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Olmesartan medoxomil

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the $AT_1$ receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An $AT_2$ 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 $AT_1$ receptor than for the $AT_2$ receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan does not inhibit ACE (kininase 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 and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. 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 plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

### 10.2 Pharmacodynamics

Olmesartan medoxomil

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

### 10.3 Pharmacokinetics

**Absorption:**

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 ($C_{max}$) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

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.

**Distribution:**

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 fetus. Olmesartan was distributed to milk at low levels in rats.

Hydrochlorothiazide

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 feces via the bile.

Hydrochlorothiazide

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

**Special Populations and Conditions**

**Pediatrics (6-16 years of age):** The pharmacokinetics of olmesartan were studied in pediatric hypertensive patients aged 6 to 16 years. The clearance of olmesartan in pediatric patients was similar to that in adult patients when adjusted by the body weight.

**Geriatrics (≥65 years of age):** 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 but statistically significant accumulation of olmesartan was observed in the elderly with repeated dosing; $AUC_{ss,\tau}$ was 33% higher in elderly patients, corresponding to an approximate 30% reduction in $CL_R$. However, the clinical relevance is unknown.

**Sex:** Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and $C_{max}$ were 10-15% higher in women than in men.

**Ethnic origin:** The antihypertensive effect of olmesartan was smaller in Black patients (usually a low- renin population), as has been seen with other ACE inhibitors, angiotensin receptor blockers and beta-blockers.

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

**Renal Insufficiency:** 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 hemodialysis has not been studied.

## 11 STORAGE, STABILITY AND DISPOSAL

Store at 15-30°C.

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

**Olmesartan Medoxomil**

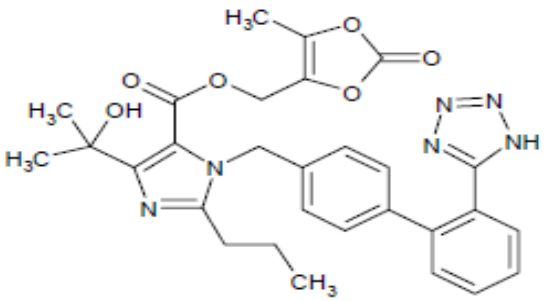
Proper name: olmesartan medoxomil

Chemical name: 1*H*-imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-,(5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester

Molecular formula: $C_{29}H_{30}N_6O_6$

Molecular mass: 558.6 g/mol

Structural formula:



Physiochemical properties: Olmesartan medoxomil is white or off white crystalline powder. It is practically insoluble in water and sparingly soluble in methanol.

**Hydrochlorothiazide**

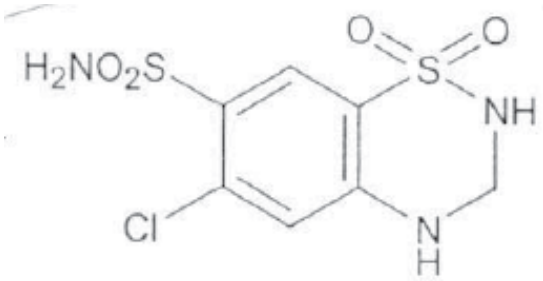
Proper name: hydrochlorothiazide

Chemical name: 6-Chloro-3,4 dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular formula: $C_7H_8ClN_3O_4S_2$

Molecular mass: 297.7 g/mol

Structural formula:




Physiochemical properties: Hydrochlorothiazide is a white or almost white crystalline powder. It is slightly soluble in water but freely soluble in sodium hydroxide solution.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

The antihypertensive effects of olmesartan medoxomil-hydrochlorothiazide have been demonstrated in clinical trials in which 1230 of 2757 patients with mild to moderate essential hypertension were exposed to a combination of olmesartan medoxomil (2.5 mg to 40 mg) and hydrochlorothiazide (12.5 mg to 25 mg). These clinical trials included one placebo-controlled factorial trial (n=502) in mild-moderate hypertensives with combinations of olmesartan medoxomil (10 mg, 20 mg, 40 mg or placebo) and hydrochlorothiazide (12.5 mg, 25 mg or placebo) for 8 weeks. Across treatment groups, the percentage of male patients ranged from 48.7% to 65.9% and the mean age ranged from 49.9 to 54.7 years. At least 58.1% in all treatment groups were Caucasian and most patients (at least 76.1%) were <65 years of age.

### 14.2 Study Results

Once-daily dosing with 20 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide, 40 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide or 40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide produced mean placebo-adjusted systolic and diastolic blood pressure reductions at trough (24 hours post-dosing) ranging from 17/8 to 24/14 mm Hg, respectively. The antihypertensive effect of the combination on trough blood pressure was related to the dose of each component (see table below). No appreciable changes in trough heart rate were observed with combination therapy in the placebo-controlled trial.

**Table 4: Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mm Hg)**

| | Olmesartan Medoxomil Dose | | | |
|---|---|---|---|---|
| HCTZ Dose | 0 mg | 10 mg | 20 mg | 40 mg |
| 0 mg | -- | 7/5 | 12/5 | 13/7 |
| 12.5 mg | 5/1 | 17/8* | 17/8* | 16/10* |
| 25 mg | 14/5 | 19/11* | 22/11* | 24/14* |

The onset of the antihypertensive effect occurred within 1 week and was near maximal at 4 weeks of treatment. All 6 dose combinations were statistically significantly more effective than placebo in lowering sitting diastolic blood pressure at Week 8 (P<0.05). The placebo-adjusted

decrease in sitting diastolic blood pressure was approximately additive as follows: 5 mm Hg to 9 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 12.5 mg HCTZ and 9 mm Hg to 14 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 25 mg HCTZ, compared to 3 mm Hg to 6 mm Hg for 10 mg to 40 mg olmesartan medoxomil alone and 2 mm Hg to 5 mm Hg for 12.5 mg to 25 mg HCTZ alone.

Results of secondary efficacy variable analysis sitting systolic blood pressure demonstrated that the 6 olmesartan medoxomil + HCTZ combinations produced effects similar to those observed for sitting diastolic blood pressure at Week 8. The reduction in systolic blood pressure generally was more pronounced than the reduction in diastolic blood pressure. The placebo-adjusted decrease in sitting systolic blood pressure was approximately additive as follows: 14 mm Hg to 17 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 12.5 mg HCTZ and 20 mm Hg to 24 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 25 mg HCTZ, compared to 7 mm Hg to 13 mm Hg for 10 mg to 40 mg olmesartan medoxomil alone and 6 mm Hg to 14 mm Hg for 12.5 mg to 25 mg HCTZ alone. Results of the analyses of standing diastolic and systolic blood pressures were consistent with those of sitting blood pressure.

The results of the responder rate analysis were consistent with the results of the analyses of the change in blood pressure from baseline to Week 8. The responder rate increased when HCTZ was combined with olmesartan medoxomil, and also increased with increasing olmesartan medoxomil and HCTZ dose. The highest responder rate (92%) was observed for the highest dose of the combination (40 mg olmesartan medoxomil + 25 mg HCTZ).

The antihypertensive effect was independent of gender, but there were too few subjects to identify response differences based on race or age greater than or less than 65 years. The blood pressure lowering effect of olmesartan medoxomil-hydrochlorothiazide combination was maintained in long-term studies for up to 2 years. The overall response to the combination treatment was similar in Black and non-Black patients in the placebo-controlled trial.

Administered doses of 10 mg, 20 mg, or 40 mg olmesartan medoxomil combined with 12.5 mg or 25 mg hydrochlorothiazide was shown to be well tolerated and statistically significantly more effective than placebo in lowering sitting diastolic blood pressure at Week 8. The magnitude of blood pressure reduction increased with increasing dose of olmesartan medoxomil and HCTZ. There was no evidence of a rebound effect in sitting diastolic blood pressure after discontinuation of olmesartan medoxomil + HCTZ.

In a supportive Phase III placebo-controlled, double-blind multi-centre study of 20 mg olmesartan medoxomil combined with either HCTZ 12.5 mg or 25 mg in patients with essential hypertension not controlled by olmesartan monotherapy, statistical significant evidence of reduction in mean daytime diastolic BP was achieved after eight weeks of combined therapy with the 25 mg HCTZ dose, but not with the 12.5 mg HCTZ dose. However, efficacy of the 12.5 mg HCTZ dose was demonstrated in eight other supportive trials.

Clinical studies of olmesartan medoxomil and hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see **CLINICAL TRIALS**).

## DETAILED PHARMACOLOGY

### Animal Pharmacology

The results of clinical and nonclinical pharmacology studies demonstrated that olmesartan, the active form of olmesartan medoxomil, is an AII receptor antagonist that binds selectively and competitively to the $AT_1$ receptor, with negligible binding to the $AT_2$ receptor. Olmesartan was shown to be both a potent and long-lasting AII antagonist in both humans and animals.

The antihypertensive effect of olmesartan depends on the activity of the renin-angiotensin system, as demonstrated by its effectiveness in different animal models of hypertension. In rat models, olmesartan is most effective in renal hypertensive rats, followed by spontaneously hypertensive rats, normotensive rats, and DOCA-salt hypertensive rats. Olmesartan also significantly decreased blood pressure in Goldblatt hypertensive Beagle dogs. The antihypertensive effect is dose-dependent and has a long duration of action. From hemodynamic studies conducted with olmesartan medoxomil, it appears that the antihypertensive effect is due to dilation of blood vessels throughout the body; however, regional blood flow in major organs is unaffected except for the kidney, where blood flow is markedly increased. It was also demonstrated that olmesartan ameliorated hypertension- and diabetic induced nephropathy in different rat models.

General pharmacology studies demonstrated that olmesartan had little effect on a variety of physiological systems, except for those that would be expected based on its pharmacology activity. Therefore, it is expected that olmesartan would produce minimal adverse effects at pharmacological doses.

Co-administration of olmesartan medoxomil and HCTZ (at ratios of 1:10 and 1:100) decreased blood pressure in spontaneously hypertensive rats to a greater extent than olmesartan medoxomil or HCTZ administered alone, indicating that there was an additive effect on blood pressure. Plasma renin activity was increased in animals treated with olmesartan medoxomil or olmesartan medoxomil/HCTZ, due to the pharmacological activity of olmesartan. Urine volume and total excretion of sodium and potassium was increased in animals treated with HCTZ or olmesartan medoxomil/HCTZ, due to the pharmacological activity of HCTZ.

### 14.3 Comparative Bioavailability Studies

A double-blinded, randomized, single-dose, two way crossover bioequivalence study comparing TEVA-OLMESARTAN / HCTZ (olmesartan medoxomil/hydrochlorothiazide) 40 mg/25 mg tablets (Teva Canada Limited) with $^{Pr}$OLMETEC PLUS® (olmesartan medoxomil/ hydrochlorothiazide) 40 mg/25 mg tablets (Merck Canada Inc.) was conducted in 63 healthy human adult Indian male subjects under fasting conditions. A summary of the bioavailability data is presented below.

**Summary Table of the Comparative Bioavailability Data for Olmesartan**

| Olmesartan<br>(1 x 40 mg/25 mg olmesartan medoxomil/hydrochlorothiazide tablet)<br>From measured data<br><br>Geometric mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | 90 % Confidence Interval |
| $AUC_T$‡<br>(ng.h/ml) | 11845.51<br>12248.1 (25.4) | 11080.25<br>11576.9 (29.1) | 106.91 | 102.657 – 111.34 |
| $AUC_\infty$<br>(ng.h/ml) | 12071.80<br>12470.9 (25.2) | 11306.495<br>11797.4 (28.7) | 106.77 | 102.62 – 111.09 |
| $C_{max}$<br>(ng/mL) | 1753.11<br>1789.7 (20.1) | 1546.60<br>1593.5 (24.4) | 113.35 | 108.67 – 118.24 |
| $T_{max}$§<br>(h) | 2.00 (1.33 – 4.50) | 2.33 (1.00 – 4.50) | | |
| $T_{½}$€<br>(h) | 8.6 (20.0) | 8.6 (21.5) | | |

* TEVA-OLMESARTAN / HCTZ (olmesartan medoxomil/hydrochlorothiazide) 40 mg/25 mg tablets (Teva Canada Limited).

† PrOLMETEC PLUS® (olmesartan medoxomil/hydrochlorothiazide) 40mg/25mg tablets (Merck Canada Inc.) were purchased in Canada

§ Expressed as the median (range) only.

€Expressed as the arithmetic mean (CV %) only.

**Summary Table of the Comparative Bioavailability Data for Hydrochlorothiazide**

| Hydrochlorothiazide<br>(1 x 40 mg/25 mg olmesartan medoxomil/hydrochlorothiazide tablet)<br>From measured data<br><br>Geometric mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | 90 % Confidence Interval |
| $AUC_T$‡ (ng.h/ml) | 1434.65<br>1471.8 (22.2) | 1391.88<br>1429.2 (21.6) | 103.07 | 99.64 – 106.62 |
| $AUC_\infty$ (ng.h/ml) | 1479.667<br>1516.4 (21.9) | 1438.30<br>1475.4 (21.4) | 102.88 | 99.56 – 106.30 |
| $C_{max}$ (ng/mL) | 198.53<br>205.3 (25.7) | 191.58<br>197.4 (23.9) | 103.63 | 99.40 – 108.03 |
| $T_{max}$§ (h) | 2.00 (0.67 – 4.50) | 1.67 (0.67 – 4.50) | | |
| $T_{½}$€ (h) | 9.6 (12.5) | 9.5 (13.4) | | |

* TEVA-OLMESARTAN / HCTZ (olmesartan medoxomil/hydrochlorothiazide) 40 mg/25 mg tablets (Teva Canada Limited).
† PrOLMETEC PLUS® (olmesartan medoxomil/hydrochlorothiazide) 40mg/25mg tablets (Merck Canada Inc.) were purchased in Canada.
§ Expressed as median (range) only.
€ Expressed as arithmetic mean (CV %) only.

## 15 MICROBIOLOGY
Not applicable

## 16 NON-CLINICAL TOXICOLOGY

**Acute Toxicity**
Olmesartan medoxomil has low oral acute toxicity in mice, rats and dogs. Doses up to 2000 mg/kg were administered to rats and mice and 1500 mg/kg to dogs with no clinical signs or mortality. Intravenous toxicity studies were conducted with olmesartan, the active metabolite, in mice and rats. Severe clinical signs occurred at all doses administered in mice (≥1700 mg/kg) and rats (≥1400 mg/kg) with lethality in mice at ≥1850 mg/kg and at ≥1550 mg/kg in rats.

**Long Term Toxicity**
Oral repeat dose toxicity studies were conducted in mice, rats and dogs with olmesartan medoxomil. Repeat dose (14-day) intravenous studies were conducted with olmesartan (the active metabolite) in rats and dogs. These studies demonstrated that olmesartan medoxomil was well tolerated at doses up to 4000 mg/kg/day in mice (90 days), 1000 mg/kg/day in rats (6 months) and 160 mg/kg/day in dogs (12 months). There were no treatment-related clinical findings at these dose levels. Severe clinicopathological effects associated with uremia necessitated the early necropsy of one dog administered 500 mg/kg (90-day study).

Hematological effects (decreased RBC count, hemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time) in rodents, clinical chemistry changes (increase in BUN and creatinine) in rodents and dogs, and histopathological findings in kidneys of rodents and dogs were observed. In kidney, hypertrophy and hyperplasia of the juxtaglomerular apparatus, accompanied by an increase in cytoplasmic granularity are considered to be due to the pharmacological effects of olmesartan on the Renin-Angiotensin System. At high doses, renal tubular regeneration was observed in rats and dogs and progressive increase in chronic neuropathy was observed in rats.

Decreased heart weights, observed in mice and rats were attributed to a decrease in heart muscle load following a reduction in blood pressure.

Saline as a water source in rats treated with olmesartan medoxomil attenuated/eliminated the observed effect.

The findings from studies in rats and dogs where olmesartan was administered IV for 14 days were consistent with the above-mentioned findings observed after oral administration.

Similarly, olmesartan medoxomil + HCTZ in combination showed effects on the kidneys which were considered to be secondary to the pharmacological activity of olmesartan and HCTZ. Oral administration of olmesartan medoxomil/HCTZ to rats for 26 weeks resulted in histopathological changes in the kidneys which were part of the spectrum of changes associated with chronic progressive nephropathy in rats. The NOAEL was 16.25 mg/kg/day in rats. The results of the 26-week oral toxicity study in dogs demonstrated that olmesartan medoxomil/HCTZ produced hypertrophy and eosinophilia of the renal tubules. The NOAEL for olmesartan medoxomil/HCTZ was 6.5 mg/kg/day for males, based on the tubular eosinophilia observed at ≥13 mg/kg/day, and 52 mg/kg/day for females.

**Mutagenicity**

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney, for clastogenicity in mouse bone marrow (micronucleus test), DNA repair in the UDS assay and DNA fragmentation in the Comet assay at oral doses of up to 2000 mg/kg.

Olmesartan medoxomil-HCTZ was negative in the *in vitro* bacterial reverse mutation test up to concentrations of 5411 µg/plate and *in vivo* mouse bone marrow micronucleus test in a ratio of 20:12.5 mg/kg, at doses up to 3144 mg/kg. There was no synergism in clastogenic activity between olmesartan medoxomil and HCTZ in combination ratios of 40:12.5, 20:12.5 and 10:12.5 µg/mL, in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay.

**Carcinogenicity**

Oncogenicity studies demonstrated that olmesartan medoxomil was not carcinogenic when administered at doses up to 2000 mg/kg/day to rats for up to 2 years (equivalent to about 480 times the maximum recommended human dose (MRHD) of 40 mg/day on a mg/ $m^2$ basis).

A 26-week oncogenicity study conducted in the transgenic mouse strain C57BL/6 TacfBR-[KO]

N5 p53(+/-) treated with up to 1000 mg/kg/day (about 120 times the MRHD) olmesartan medoxomil revealed no evidence of carcinogenic potential. No carcinogenicity studies were conducted with olmesartan medoxomil and hydrochlorothiazide.

**Hydrochlorothiazide**
According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheocytochroma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential in vivo, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

**Reproduction Studies**
There was no effect on fertility in rats at doses up to 1000 mg/kg/day (240 times the MRHD) of olmesartan medoxomil. No teratogenic effects and no significant effects on the number of corpora lutea, implants and dead/live fetuses were observed in rats at doses up to 1000 mg/kg/day and in rabbits at doses up to 1 mg/kg/day. Perinatal/postnatal toxicity studies in rats demonstrated that a NOAEL for developmental toxicity is 0.3 mg/kg/day of olmesartan medoxomil.

Olmesartan/HCTZ had no effect on embryo-fetal development in mice. Embryo-fetal toxicity studies conducted in rats treated with olmesartan medoxomil/HCTZ at doses up to 1625 mg/kg/day produced developmental delays related to the extent of maternal toxicity; the developmental NOAEL for this effect was 162.5 mg/kg/day. No perinatal/postnatal studies were conducted with olmesartan medoxomil/HCTZ.

## 17 SUPPORTING PRODUCT MONOGRAPHS

1. OLMETEC PLUS® (Tablet, 20mg/12.5mg, 40mg/12.5mg and 40mg/25mg), submission control 250557, Product Monograph, Organon Canada Inc. (April 27, 2021)

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

# $^{Pr}$TEVA-OLMESARTAN / HCTZ

Olmesartan Medoxomil and Hydrochlorothiazide Tablets

**Read this carefully before you start taking TEVA-OLMESARTAN / HCTZ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TEVA-OLMESARTAN / HCTZ.**

**Serious Warnings and Precautions – Pregnancy**

TEVA-OLMESARTAN / HCTZ should not be used during pregnancy. Taking TEVA-OLMESARTAN / HCTZ during pregnancy can cause harm and even death to your baby. If you discover that you are pregnant while taking TEVA-OLMESARTAN / HCTZ, stop the medication as soon as possible and contact your doctor.

## What is TEVA-OLMESARTAN / HCTZ used for?

TEVA-OLMESARTAN / HCTZ is used to lower blood pressure in adults.

## How does TEVA-OLMESARTAN / HCTZ work?

TEVA-OLMESARTAN / HCTZ contains a combination of two drugs, olmesartan medoxomil and hydrochlorothiazide:

- Olmesartan medoxomil is an angiotensin receptor blocker (ARB). It acts to prevent the hormone in your body that causes the blood vessels to constrict. It lowers blood pressure by relaxing the blood vessels.
- Hydrochlorothiazide is a diuretic or “water pill”. This lowers blood pressure by increasing urination.

TEVA-OLMESARTAN / HCTZ does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking TEVA-OLMESARTAN / HCTZ regularly even if you feel fine.

## What are the ingredients in TEVA-OLMESARTAN / HCTZ?

Medicinal ingredients: Olmesartan medoxomil and hydrochlorothiazide

Non-medicinal ingredients: hydroxypropylcellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, triacetin, red iron oxide, sunset yellow FCF aluminum lake (20 mg/12.5 mg and 40 mg/12.5 mg only), and yellow iron oxide.

## TEVA-OLMESARTAN / HCTZ comes in the following dosage forms:

Tablets: 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg.

## Do not use TEVA-OLMESARTAN / HCTZ if you:

- Are allergic to olmesartan medoxomil, hydrochlorothiazide or to any of the other ingredients of TEVA-OLMESARTAN / HCTZ
- Are allergic to any sulphonamide-derived drugs. Most of them have a medicinal ingredient that ends in "**-MIDE**".
- Have experienced an allergic reaction with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing to any ARB (Angiotensin Receptor Blocker). You can recognize an ARB because its medicinal ingredient ends in "**-SARTAN**". Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have problems passing urine or produce no urine.
- Are pregnant or intend to become pregnant. Taking TEVA-OLMESARTAN / HCTZ during pregnancy can cause harm and even death to your baby.
- Are breastfeeding. It is possible that TEVA-OLMESARTAN / HCTZ passes into breast milk.
- Have diabetes or kidney disease and are already taking medicine that contains aliskiren (such as Rasilez), which is used to lower high blood pressure.
- Have one of the following rare hereditary diseases
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-OLMESARTAN / HCTZ. Talk about any health conditions or problems you may have, including if you:**

- Have a greater chance of developing skin cancer because you:
    - had skin cancer or have a family history of skin cancer.
    - have light-coloured skin
    - sunburn easily
    - take drugs to suppress your immune system
- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors
- Are allergic to the penicillin (antibiotic drug)
- Have a narrow artery or a heart valve.
- Had a heart attack or have heart or blood vessel disease
- Had a stroke or have a condition that affects the blood supply to the brain.
- Have liver or kidney disease
- Have blocked bile ducts
- Are taking a medicine that contains aliskirin, such as Rasilez, used to lower high blood pressure. The combination with TEVA-OLMESARTAN / HCTZ is not recommended.
- Are taking an angiotensin converting enzyme inhibitor (ACE inhibitors). You can recognize ACE inhibitors because their medicinal ingredient ends in "**-PRIL**".
- Have lupus or gout.
- Have diabetes
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are on a low-salt diet.
- Are less than 18 years old.
- Have asthma
- Are taking any medication including non-prescription or herbal products.
- You have to undergo any kind of surgery and general anesthesia.

**Other warnings you should know about:**

TEVA-OLMESARTAN / HCTZ can:

- cause severe chronic diarrhea with substantial weight loss (sprue-like enteropathy). It can take months to years for symptoms to develop.
- lower the levels of sodium, chloride and potassium in the blood.

**Pregnancy:**
TEVA-OLMESARTAN / HCTZ can cause harm to your unborn baby. Taking TEVA-OLMESARTAN / HCTZ during pregnancy can:

- prevent the normal growth of your baby's kidneys and skull if you take the drug during the second and third trimester. Your doctor may recommend an ultrasound.
- cause your baby's eyes and skin to turn yellow after birth.
- lower the level of platelets in your baby's blood.

**Risk of skin cancer:**
TEVA-OLMESARTAN / HCTZ contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking TEVA-OLMESARTAN / HCTZ for many years (more than 3) or at a high dose.

While taking TEVA-OLMESARTAN / HCTZ:

- Make sure to regularly check your skin for any new lesions (such as a lump, bump, sore, or patch). Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back. Talk to your doctor immediately if you develop new skin lesions
- Limit your exposure to the sun and to indoor tanning.
- Always use sunscreen (SPF-30 or higher)
- Protect your skin when going outside by covering your skin with clothing and a hat.
- You may become sensitive to the sun. Talk to your doctor immediately if you get more sensitive to the sun or UV light.

**Hydrochlorothiazide in TEVA-OLMESARTAN / HCTZ can cause Sudden Eye Disorders. These disorders can develop within hours to weeks of starting TEVA-OLMESARTAN / HCTZ.**

- **Sudden Myopia (nearsightedness):** objects further away appear blurry.
- **Sudden Glaucoma:** blurred vision increased pressure in your eyes, and eye pain. It may lead to permanent vision loss if left untreated.

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to TEVA-OLMESARTAN / HCTZ. Dizziness, lightheadedness, or fainting can occur when you take the drug for after the first time and when your dosage is increased.

Avoid drinking alcohol until you have discussed this with your doctor. Drinking alcohol may lower your blood pressure and may cause you to feel sudden dizziness when you stand up.

If you take TEVA-OLMESARTAN / HCTZ with medicines that reduce pain and swelling (Non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors), you may experience:

- A decline in kidney function or sudden kidney failure. Contact your doctor and go to the emergency department immediately if you notice:
  - a decrease in the amount of urine you produce
  - generalized swelling
  - weakness
  - shortness of breath, or irregular heartbeats
  - loss of appetite
  - lethargy, and fatigue

- A decrease in the ability of TEVA-OLMESARTAN / HCTZ to lower your blood pressure. This means that TEVA-OLMESARTAN / HCTZ may not be able to lower your blood pressure as it is expected to do. If this happens, speak with your doctor or pharmacist.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

As with most medications, interaction with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

**The following may interact with TEVA-OLMESARTAN / HCTZ:**

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome
- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”)
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications).
- Amantadine
- Amphotericin B, an antifungal drug.
- Anesthetics
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Anticholinergic agents
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Blood pressure-lowering drugs, including diuretics (“water pills”), aliskiren-containing products (e.g. Rasilez), or angiotensin converting enzyme inhibitors ACE inhibitors.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine
- Digoxin, a heart medicine.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used for arthritis and to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib (COX-2 Inhibitor).
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare.
- Pressor amines such as norepinephrine.
- Sympathomimetics

**How to take TEVA-OLMESARTAN / HCTZ**

- Take TEVA-OLMESARTAN / HCTZ exactly as prescribed. Do NOT take more of it than prescribed.
- It is recommended to take your dose at about the same time every day.
- TEVA-OLMESARTAN / HCTZ is not for initial treatment.
- TEVA-OLMESARTAN / HCTZ may be taken with or without food.

**Usual dose:**

Take one tablet daily. More than one tablet daily is not recommended.

**Overdose:**

If you think you, or a person you are caring for, have taken too much TEVA-OLMESARTAN / HCTZ contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

**What are possible side effects from using TEVA-OLMESARTAN / HCTZ?**

These are not all the possible side effects you may feel when taking TEVA-OLMESARTAN / HCTZ. If you experience any side effects not listed here, contact your doctor.
Side effects may include:

- Back pain
- Decreased appetite
- Dizziness, headache
- Fatigue
- Gastrointestinal problems:
- Constipation
- Diarrhea
- Nausea
- Upset stomach
- Vomiting
- Joint pain
- Muscle cramps, spasms and pain
- Rash, red itchy patches on the skin
- Restlessness and weakness
- Upper respiratory tract infection
- congested and runny nose
- cough
- sore throat

**If any of these affects you severely, tell your doctor, nurse or pharmacist.**

TEVA-OLMESARTAN / HCTZ can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **COMMON** | | | |
| **Ear Disorder** (Vertigo): a sense of dizziness, spinning | | √ | |
| **Urinary Track Infections:** difficulty and pain when passing urine, exaggerated sense of needing to urinate, blood in urine and cloudy urine | | √ | |
| **Non-melanoma skin cancer:** lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly. | | √ | |
| **Hematuria** (blood in urine): pink, red or very dark urine | | √ | |
| **High blood sugar:** frequent urination, increased thirst, dry skin, headache, blurred vision and fatigue | √ | | |
| **Low Blood Pressure:** dizziness, fainting, lightheadedness | √ | | |
| **Chest Pain:** Painful pressure or tightness in your chest | √ | | |
| **Edema:** Unusual swelling of the arms, legs, ankles or feet. | √ | | |
| **Allergic Reaction:** rash, hives, swelling of the lips, face, tongue or throat difficulty swallowing or breathing. | | | √ |
| **UNCOMMON** | | | |
| **Kidney Disorder:** change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue. | | √ | |
| **Liver Disorder:** yellowing of the skin or eyes, dark urine, | | √ | |

| | | | |
|---|---|---|---|
| abdominal pain, nausea, vomiting, loss of appetite. | | | |
| **RARE** | | | |
| **Acute Kidney Failure:** decrease or absence of urine, generalized swelling, weakness, shortness of breath, or irregular heartbeats, loss of appetite, lethargy and fatigue). | | | √ |
| **Increased levels of potassium in the blood:** irregular heartbeats, muscle weakness and generally feeling unwell | | √ | |
| **Rhabdomyolysis** (breakdown of damaged muscles): muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine. | | √ | |
| **Palpitation** (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly. | √ | | |
| **UNKNOWN** | | | |
| **Anemia** (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath. | | √ | |
| **Sprue-like enteropathy:** severe chronic diarrhea with substantial weight loss. | | √ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
You can report any suspected side effects associated with the use of health products to Health Canada by:

Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store at 15-30°C.

Keep out of reach and sight of children.

**If you want more information about TEVA-OLMESARTAN / HCTZ:**

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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