Passion for Innovation.
Compassion for Patients.™

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TRIBENZOR®
(olmesartan medoxomil, amlopdipine, hydrochlorothiazide)
Fact Sheet

- **TRIBENZOR®** (olmesartan medoxomil, amlodipine, hydrochlorothiazide) is a three-in-one combination product indicated for the treatment of hypertension. **TRIBENZOR** is not indicated for initial therapy.

- The U.S. Food and Drug Administration (FDA) granted marketing approval for **TRIBENZOR** in July 2010. **TRIBENZOR** is marketed by Daiichi Sankyo, Inc.

Importance of Hypertension Control

- Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (heart attacks). These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class to which **TRIBENZOR** principally belongs. There are no controlled trials demonstrating risk reduction with **TRIBENZOR**.

- Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals.

Mechanism of Action

- **TRIBENZOR** combines three widely prescribed antihypertensive medications, each working in a different way, to lower blood pressure.

- **TRIBENZOR** combines the complementary actions of olmesartan medoxomil (which blocks binding of angiotensin II to the AT_1 receptor), amlodipine (which inhibits the entrance of calcium into the blood vessel walls), and hydrochlorothiazide (a diuretic which reduces water volume in the blood). Together these three medicines allow blood vessels to relax and help reduce the amount of volume in the blood so that blood can flow more easily.

Clinical Data

- After eight weeks of treatment, **TRIBENZOR** 40/10/25 mg produced statistically significantly greater reductions in both systolic and diastolic blood pressures compared to each of the three dual combination therapies.[1]

- According to the **TRIBENZOR** pivotal registration trial that included a total of 2,492 patients with hypertension (mean baseline blood pressure 168.5/100.9 mm Hg), the switch to **TRIBENZOR** 40/10/25 mg from each of the following three dual combination therapies: (i) amlodipine/

hydrochlorothiazide 10/25 mg, (ii) olmesartan/hydrochlorothiazide 40/25 mg, and (iii) olmesartan/ amlodipine 40/10 mg, yielded a further mean reduction after eight weeks of treatment in systolic blood pressure/diastolic blood pressure of 8.1/5.4 mm Hg, 7.6/5.4 mm Hg, and 8.4/4.5 mm Hg, respectively (all highly statistically significant). As this was an active-controlled trial, these treatment effects include a placebo effect of unknown size.

- The most frequently reported adverse reaction was dizziness. Dizziness occurred in 5.8 percent to 8.9 percent of subjects who were switched from dual therapy to **TRIBENZOR**, vs 1.4 percent to 3.6 percent of subjects who remained on dual therapy. The other most frequent adverse reactions occurring in greater than or equal to two (2) percent of patients treated with **TRIBENZOR** were peripheral edema (7.7 percent), headache (6.4 percent), fatigue (4.2 percent), nasopharyngitis (3.5 percent), muscle spasms (3.1 percent), nausea (3.0 percent), upper respiratory tract infection (2.8 percent), diarrhea (2.6 percent), urinary tract infection (2.4 percent), and joint swelling (2.1 percent).

Dose Strength

- There are currently five approved doses of **TRIBENZOR**, which contain the following dose strength combinations of olmesartan medoxomil / amlodipine / hydrochlorothiazide.

  - 20 / 5 /12.5 mg
  - 40 / 5/ 12.5 mg
  - 40/ 5/ 25 mg
  - 40/ 10/ 12.5 mg
  - 40/ 10/ 25 mg

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Important Safety Information for TRIBENZOR®

WARNING: FETAL TOXICITY
- **When pregnancy is detected, discontinue TRIBENZOR as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS AND PRECAUTIONS: Fetal Toxicity**

CONTRAINDICATIONS

Do not co-administer aliskiren with TRIBENZOR in patients with diabetes.
TRIBENZOR is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Fetal Toxicity: TRIBENZOR is **Pregnancy Category D**.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with TRIBENZOR.

Impaired Renal Function: Monitor for worsening renal function in patients with renal impairment while on TRIBENZOR.

In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Similar results may be anticipated in patients treated with TRIBENZOR.

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, and similar results may be expected with TRIBENZOR.

Avoid use of TRIBENZOR in patients with severely impaired renal function (creatinine clearance ≤30 mL/min). If progressive renal impairment becomes evident, consider withholding or discontinuing TRIBENZOR.

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, exclude other etiologies. Consider discontinuation of TRIBENZOR in cases where no other etiology is identified.

Hepatic Impairment: Initial therapy with TRIBENZOR is not recommended in hepatically impaired patients. In patients with severe hepatic impairment, avoid use of TRIBENZOR. Thiazides (a component in TRIBENZOR) 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.

Electrolyte and Metabolic Imbalances: Due to the hydrochlorothiazide (HCTZ) component in TRIBENZOR, observe patients for clinical signs of metabolic, fluid, or electrolyte imbalance.

Hypersensitivity Reaction: Hypersensitivity reactions to HCTZ (a component in TRIBENZOR) may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus: Thiazides (a component in TRIBENZOR) have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Acute Myopia and Secondary Angle-Closure Glaucoma: Thiazides can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Discontinue HCTZ (a component in TRIBENZOR) as rapidly as possible in these patients.

Vasodilation: Although vasodilation attributable to amlodipine (a component in TRIBENZOR) is gradual in onset, acute hypotension has rarely been reported after oral administration. Patients with severe aortic stenosis may be at particular risk.

Increased Angina and/or Myocardial Infarction: Patients taking TRIBENZOR, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of

angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dose increase.

Laboratory Tests: Lab abnormalities may include increased blood creatinine levels and hyperkalemia (olmesartan medoxomil), hepatic enzyme elevations (amlodipine), and increased cholesterol and triglyceride levels (HCTZ).

DRUG INTERACTIONS

Non-Steroidal Anti-Inflammatory Agents: Concurrent administration of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to increased risk of renal impairment (including possible acute renal failure) and loss of antihypertensive effect of TRIBENZOR.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, 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, avoid combined use of RASinhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on TRIBENZOR and other agents that affect the RAS.

Avoid use of aliskiren with TRIBENZOR in patients with renal impairment (GFR <60 mL/min).

Concurrent Use with Colesevelam Hydrochloride: Concurrent administration of colesevelam hydrochloride with TRIBENZOR reduces the systemic exposure and peak plasma concentration of olmesartan. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Effect of Amlodipine on Simvastatin: Due to increased exposure to simvastatin, when co-administered with amlodipine (a component in TRIBENZOR), do not exceed doses of greater than 20 mg daily of simvastatin.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of olmesartan or thiazide diuretics. Monitor lithium levels in patients receiving TRIBENZOR and lithium.

ADVERSE REACTIONS

The most frequently reported adverse reaction was dizziness (5.8% to 8.9%). The other most frequent adverse reactions occurring in ≥2% of patients treated with TRIBENZOR were peripheral edema (7.7%), headache (6.4%), fatigue (4.2%), nasopharyngitis (3.5%), muscle spasms (3.1%), nausea (3.0%), upper respiratory tract infection (2.8%), diarrhea (2.6%), urinary tract infection (2.4%), and joint swelling (2.1%).

USE IN SPECIFIC PATIENT POPULATIONS

Nursing Mothers: Avoid use while nursing; discontinue either nursing or the drug.

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Please see Prescribing Information for TRIBENZOR.

Reference:
[1] Oparil S, Melino M, Lee J, Fernandez BS, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine, besylate, and hydrochlorothiazide in adult patients with hypertension: the TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. 2010;32:1252-1269.