Amlodipine/Olmesartan Medoxomil (Azor)

**Manufacturer:** Daiichi Sankyo, Parsippany, NJ  
**Indication:** Amlodipine besylate plus olmesartan medoxomil is indicated for the treatment of hypertension, alone or with other antihypertensive agents. It is not indicated for the initial therapy of hypertension.

**Drug Class:** This product combines the complementary actions of the calcium-channel blocker amlodipine, which inhibits the entrance of calcium into the blood vessel walls, and of those of olmesartan, which blocks angiotensin II receptors. Angiotensin II is a hormone that causes blood vessels to constrict.

**Uniqueness of Drug:** Azor relaxes the blood vessels so that blood can flow more easily. The two agents have been found to produce significant mean reductions in systolic and diastolic blood pressure in patients with hypertension.

**Black-Box Warning:** When used in pregnancy during the second and third trimesters, drugs that act directly on the renin–angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Azor should be discontinued as soon as possible.

**Warnings and Precautions:** In volume-depleted or salt-depleted patients, symptomatic hypotension resulting from the olmesartan component in particular may occur after the drug is initiated. Treatment should start with patients under close medical supervision.

Patients, particularly those with severe obstructive coronary artery disease, may experience an increased frequency, duration, or severity of angina or acute myocardial infarction (MI) when beginning calcium-channel blocker therapy.

In studies of angiotensin-converting enzyme (ACE)–inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. No data are available for the long-term use of olmesartan in patients with unilateral or bilateral renal artery stenosis, but similar effects would be expected with amlodipine/olmesartan because of the olmesartan component.

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with severely impaired hepatic function, caution should be exercised in patients with severe hepatic impairment.

The only adverse event that occurred in more than 3% of treated patients, and more frequently than with placebo, was edema (22.2% with Azor vs. 12.3% with placebo).

**Safety Information about Olmesartan:**

**Use in Pregnancy:** Drugs that act directly on the renin–angiotensin system can cause injury and even death to the developing fetus when they are used in pregnancy during the second and third trimesters. When pregnancy is confirmed, olmesartan should be discontinued as soon as possible.

**Hypotension in Volume- or Salt-Depleted Patients:** In patients with an activated renin–angiotensin system, such as those with volume or salt depletion (e.g., if they are receiving high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Azor. Treatment should be initiated with patients under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should be given an intravenous (IV) infusion of normal saline solution. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty after the blood pressure has stabilized.

**Impaired Renal Function:** In studies of ACE-inhibitors in patients with unilateral or bilateral renal artery stenosis, elevated serum creatinine or BUN levels have been reported. There are no data on the long-term use of olmesartan in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

**Dosage and Administration:** Azor may be substituted for its individually titrated components for patients receiving amlodipine and olmesartan. Azor may also be used as add-on therapy for patients whose hypertension is not adequately controlled with amlodipine or olmesartan therapy.

The dosage may be increased after two weeks to a maximum dose of 10/40 mg once daily, usually, with one component increased at a time. The amounts of both components may be raised to achieve more rapid control. Maximum antihypertensive effects are attained within two weeks after a change in the dose.

Azor tablets are formulated for oral administration as shown in Table 1. The dosage may be increased after two weeks. The maximum recommended dose of the combination product is 10/40 mg.

**Commentary:** Hypertension is one of the most prevalent conditions in the U.S. It affects almost one in three American adults and about one billion people worldwide. It is often difficult to control. Only about 35% of patients with a diagnosis of high blood pressure have the condition under control.

Both components of Azor have established clinical efficacy and a favorable side-effect profile. The product provides two complementary mechanisms of action to lower blood pressure. Together the two medications relax the blood vessels so that blood can flow more effectively. The combination should

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**Table 1: Amlodipine/Olmesartan Medoxomil (Azor) Formulations**

<table>
<thead>
<tr>
<th>Amlodipine equivalent</th>
<th>Olmesartan medoxomil equivalent</th>
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<tbody>
<tr>
<td>5/20 mg</td>
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<tr>
<td>5/40 mg</td>
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<td>10/40 mg</td>
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The author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His e-mail address is MarvinMGoldenberg@verizon.net.
Human thrombin is derived from human plasma obtained from carefully screened and tested U.S. donors. The product has undergone steps to reduce the risk of transfusion-transmitted diseases.

	
give physicians a new option for treating blood pressure that remains too high with currently prescribed drugs.

Sources: www.azor.com; www.medicalnewstoday.com/articles/83920.php

**Dexrazoxane HCl for Injection (Totect)**

**Manufacturer:** TopoTarget A/S, Copenhagen, Denmark

**Indication:** Totect is used to treat extravasation resulting from IV anthracycline agents used in chemotherapy. Anthracyclines (e.g., daunorubicin, doxorubicin, and epirubicin) constitute one of the cornerstones in the treatment of breast cancer and leukemia. Extravasation occurs when injected drugs leak out of the vein and into the skin.

**Drug Class:** The formula for dexrazoxane is (S)-4,4´-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione. A potent intracellular chelating agent, it is a derivative of ethylenediamine tetraacetic acid (EDTA).

**Uniqueness of Drug:** A metal ion chelator, dexrazoxane is also a catalytic inhibitor of DNA topoisomerase II. However, the mechanism of action that protects against the extravasation of anthracycline is not known. Topoisomerase enzymes are essential for cell growth and proliferation, and they are the target of a group of anticancer chemotherapeutics (the anthracyclines). Totect blocks the activity of the topoisomerase enzyme and prevents the effect of anthracyclines.

**Warnings:**

**Pregnancy Category D:** Dexrazoxane was toxic to pregnant rats at doses of 2 mg/kg (one-eighth of the human dose defined in milligrams per square meter [mg/m²]) and embryotoxic and teratogenic at a dose of 8 mg/kg (about half the human dose on a mg/m² basis) when given daily during the period of organogenesis. Teratogenic effects in the rat included an imperforate anus, microphthalmia, and anophthalmia.

In offspring that developed to maturity, fertility was impaired in male and female rats treated in utero during organogenesis at a dose of 8 mg/kg. In rabbits, a dose of 5 mg/kg daily (about one-sixteenth of the human dose on a mg/m² basis) during the period of organogenesis caused maternal toxicity and a dose of 20 mg/kg (one-fourth the human dose on a mg/m² basis) was embryotoxic and teratogenic. Teratogenic effects in the rabbit included several skeletal malformations such as a short tail, rib and thoracic malformations, and soft-tissue variations as well as agenesis of the gallbladder and of the intermediate lobe of the lung.

There is no adequate information about the use of Totect in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

**Precautions:** Dexrazoxane HCl is cytotoxic. When given to patients receiving anthracycline-containing cytotoxic therapy, additional cytotoxicity may occur. Totect is associated with leukopenia, neutropenia, and thrombocytopenia. Hematological monitoring should be performed. Reversible elevations of liver enzymes may occur with dexrazoxane.

Greater exposure to dexrazoxane may occur in patients with compromised renal function. Blood counts and liver enzymes should be monitored.

**Dosage and Administration:** Totect should be given once daily for three consecutive days (Table 2). The first infusion should be initiated as soon as possible and within the first six hours after extravasation. The dose should be reduced by 50% in patients with creatinine clearance values below 40 mL/minute.

**Commentary:** Totect received orphan drug status. This is the only approved drug for the treatment of extravasation resulting from IV anthracycline chemotherapy. It is used as therapy when IV anthracycline accidentally leaks into the surrounding healthy tissue.

Source: www.fda.gov

**Topical (Human) Thrombin (Evithrom)**

**Manufacturer:** Omrix Biopharmaceuticals Ltd., Oak Island, NC

**Indications:** Used topically, Evithrom is a blood-clotting protein that aids hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and when control of bleeding by standard surgical techniques is ineffective or impractical. It may be used in conjunction with an absorbable gelatin sponge.

**Drug Class:** Human thrombin is derived from human plasma obtained from carefully screened and tested U.S. donors. The product has undergone steps to reduce the risk of transfusion-transmitted diseases.

**Uniqueness of Drug:** Thrombin helps to control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and is the only product currently licensed.

**Warnings and Precautions:** Made from human plasma, Evithrom may carry a risk of transmitting infectious agents, such as viruses and, theoretically, the Creutzfeldt–Jakob disease agent. The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain virus infections, and by inactivating and removing certain viruses.

Despite these measures, thrombin products still have the potential to transmit disease. It is also possible that unknown infectious agents may be present in these products. Physicians and other health care providers should report all infections suspected to have been transmitted by Evithrom to the company. Physicians should discuss the risks and benefits of this product with their patients. There is a potential risk of thrombosis if it is absorbed systemically.

**Dosage and Administration:**

**Before application:** Thrombin should be thawed by one of these methods:

- 2° to 8° C (in the refrigerator): Vials thaw within one day.
- 20° to 25° C (at room temperature): Vials thaw within one hour.

### Table 2 Dosage for Dexrazoxane (Totect)

<table>
<thead>
<tr>
<th>Recommended Dose</th>
<th>Maximum Recommended Dose</th>
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<tbody>
<tr>
<td>Day one: 1,000 mg/m²</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Day two: 1,000 mg/m²</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Day three: 500 mg/m²</td>
<td>1,000 mg</td>
</tr>
</tbody>
</table>
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- 37°C for 2-mL and 5-mL vials only: Vials thaw within 10 minutes and must not be left at this temperature for longer than 10 minutes. The temperature must not exceed 37°C.

The flip-off plastic cap should be removed from the vial to expose the rubber stopper. With a sterile needle and syringe, the thrombin solution may be withdrawn from the glass vial. Alternatively, using aseptic techniques, the practitioner can remove the rubber stopper by removing the metal pull tab to transfer the thrombin into a sterile container.

Thrombin is used topically and should be applied on the surface of bleeding tissue only. It should not be injected.

**Thrombin alone:**

- The target surface should be sponged (not wiped) or suctioned free of blood before the product is applied.
- A sterile syringe and small-gauge needle may be used to flood the surface with thrombin.
- After treatment, the clot should not be sponged to ensure that it remains securely in place.

**Thrombin in conjunction with an absorbable gelatin sponge:**

- Using aseptic technique, the practitioner transfers the thrombin into a sterile container.
- The gelatin sponge, in its desired shape, is immersed in the thrombin solution.
- The practitioner vigorously kneads the sponge with moistened gloved fingers until all air is expelled and the sponge can return to its original size and shape.
- The saturated sponge is held in place with a gauze or cotton pledget. Moderate pressure is applied until hemostasis is achieved. The amount of thrombin required depends upon the area of tissue to be treated and the method of application. As an approximate guide, volumes up to 10 mL were used in clinical studies in which thrombin was used in conjunction with an absorbable gelatin sponge.

Vials are for a single use only. Unused contents must be discarded.

**Dosage Forms and Strengths:** Vials contain 2 mL, 5 mL, or 20 mL. Each vial contains 800 to 1200 IU/mL of Evithrom.

**Commentary:** Topical human thrombin is a manufactured human plasma-derived alternative to the use of bovine protein-based thrombin, which is currently used to control bleeding in approximately one million surgical procedures each year in the U.S. Exposure to bovine-derived thrombin sometimes produces an immunogenic response in some patients. In patients who develop antibodies to bovine-derived thrombin, there is an increased risk of severe bleeding, thrombosis, anaphylactic shock, and an immunogenic response if they are re-exposed to these products.

Evithrom helps stop oozing and minor bleeding from capillaries and small veins when control of bleeding by standard surgical techniques is not feasible. The product is applied to the surface of bleeding tissue, and it may be used along with an absorbable gelatin sponge.

**Source:** www.fda.gov