Both are for adjuvant treatment of HER2-overexpressing, node-positive, or high-risk node-negative breast cancer.

Specifically, trastuzumab is a chimeric human–murine MAb that binds to the HER2 (or c-erbB2) protooncogene found on the surface of normal cells and plays a role in regulating cell growth. In the case of metastatic breast cancer cells, approximately 25% to 30% of tumors overexpress excess amounts of HER2. Thus, only patients who have tumors with this characteristic have shown benefit from trastuzumab. It should be used to treat only tumors that have HER2 protein overexpression. The trastuzumab–paclitaxel cycle is 21 days of treatment for six cycles.

The labeling of trastuzumab contains a black box warning regarding the risk of ventricular dysfunction and congestive heart failure (CHF). The patient receiving this medicine must be monitored closely. The recommended loading dose is 4 mg/kg as a 90-minute intravenous infusion along with 175 mg/m^2/dose on day 1 of therapy and must not be administered as an IV push or bolus. Subsequent weekly 2 mg/kg doses of trastuzumab can be administered as a 30-minute IV infusion if the first infusion was well tolerated on days 8 and 15 except for day 1 of the first cycle. Herceptin is available in a 440 mg/21 mL multidose vial and can be administered in an outpatient setting. Reconstituted trastuzumab must be discarded after 28 days.

TISSUE PLASMINOGEN ACTIVATORS

tPAs are substances produced in small quantity by the inner lining of blood vessels and by the muscular wall of the uterus. They prevent abnormal blood clotting by converting plasminogen, a component of blood, to the enzyme plasmin, which breaks down fibrin, the main constituent of a blood clot.

Genetic engineering has prepared these substances artificially, and they are used as *thrombolytic agents* (agents that dissolve blood clots). They are used for conditions such as heart attack, angina, and occluded arteries. Unlike other anticoagulant drugs, tPA acts only on the site of the clot.

Recombinant Alteplase (Activase)

Alteplase, a tPA produced by rDNA, is used in the management of acute myocardial infarction (AMI), acute ischemic stroke, and pulmonary embolism (PE). It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA for natural human tissue-type plasminogen activator obtained from a human melanoma cell line.

The biologic activity of alteplase is determined by an in vitro clot lysis assay. The activity is expressed in IUs as tested against the WHO standard. Its specific activity is 580,000 IU/mg. Alteplase is an enzyme (serine protease) that has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When administered, alteplase binds to fibrin in a thrombus and converts the trapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis.

An appropriate volume of the accompanying sterile water for injection (without preservatives) is added to the vial containing the lyophilized powder (2, 50, or 100 mg) (Fig. 19.16). Reconstitution should be with a large-bore (e.g., 18 gauge) needle and the stream of sterile water for injection directed into the lyophilized cake. A slight foaminess can be expected; when allowed to stand undisturbed, it should dissipate within several minutes. The resultant solution appears as a colorless to pale yellow transparent solution having a pH of approximately 7.3 and containing 1 mg/mL.

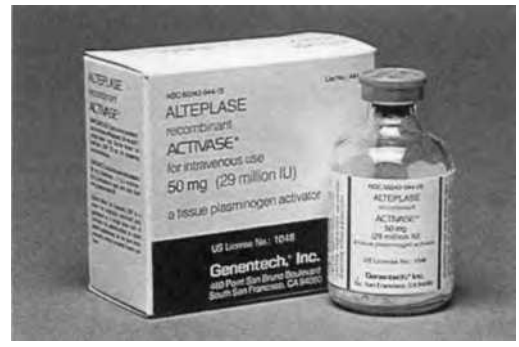

FIGURE 19.16 The product package of Activase (Alteplase). (Courtesy of Genentech, Inc.)