

POLICY & PRACTICE

Counterfeit Lipitor

The Food and Drug Administration is alerting U.S. physicians and patients to a recent recall of a batch of counterfeit "Lipitor" (atorvastatin) that was sold in the United Kingdom. U.S. consumers who purchased FDA-approved Lipitor through legitimate U.S. pharmacies should not have received the counterfeit medicine, according to the FDA. However, consumers may have received counterfeit pills if they obtained drugs from the United Kingdom via online or storefront operations that do not supply FDA-approved products, or

through state-run drug importation programs that facilitate the purchase of foreign drugs. Initial testing of the counterfeit drug by U.K. health officials showed that the product does not pose an immediate risk to patients. However, the FDA is advising patients that there is no guarantee of quality or effectiveness. Patients who have the counterfeit Lipitor should stop using it and consult their physician or pharmacist if they have questions or concerns. The counterfeit tablets are 20 mg and are sold in packages of 28 tablets. The batch number is 004405K1 with an expi-

ration date of "11 2007." Legitimate doses of Lipitor sold in Britain also have the same batch number, the FDA reported.

Chronic Care Pilots

Medicare is launching chronic care pilot projects this year aimed at improving care for people with heart failure and diabetes. The program, called Medicare Health Support, will provide free, voluntary services to about 160,000 Medicare fee-for-service beneficiaries for 3 years. Participating patients will get access to nurse coaches, reminders about preventive care needs, prescription drug counseling, home visits and intensive care management when needed,

and home monitoring equipment to track health status. At press time, eight areas had been selected for the program: Maryland, Oklahoma, Western Pennsylvania, Mississippi, Northwest Georgia, Chicago, Central Florida, and Washington, D.C. "We are providing beneficiaries additional tools to help them manage their health more effectively and avoid preventable complications," Health and Human Services Secretary Mike Leavitt said in a statement.

Heart Trials and Women

More women should be recruited to participate in clinical trials of heart disease to have "statistically sufficient power" to identify whether women respond differently to treatment than men, according to a study published in August in the *European Heart Journal* (2005;26:1585-95). The study analyzed the existing literature on female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. The authors recommended that researchers analyze data on hormonal aspects, such as concomitant hormone therapy; gender differences in pharmacodynamics and in complication rates should be incorporated as well. "It is essential that trials are designed to provide the necessary data so that researchers know from the outset that they will be able to analyze factors that could contribute to different outcomes for men and women," Verena Stangl, M.D., a cardiologist in Berlin and senior author of the study, said in a statement.

Taking Obesity Seriously

Most Americans are still taking obesity seriously as a public health problem, despite recent studies indicating that health risks may have been overstated, according to a survey designed by the Harvard School of Public Health in Boston. Only 15% of Americans surveyed said they believed that the health risks of obesity were being overestimated by scientific experts. In fact, 58% said that they thought the experts were portraying the risks accurately, and 22% thought the risks of obesity were being underestimated. And despite the conflicting research results, Americans are continuing to track calories, fat content, and carbohydrates at about the same rate as last year, Robert J. Blendon, M.D., and his colleagues reported. Julie Gerberding, M.D., director of the Centers for Disease Control and Prevention, said in a statement she was encouraged by the results of the poll.

Clinician's Guide to Alcoholism

Physicians have a new tool to help them identify and care for patients with heavy drinking and alcohol use disorders. About 3 in 10 U.S. adults drink at levels that increase their risk for physical, mental health, and social problems. Of these heavy drinkers, about one in four currently has alcohol dependence problems that often go undetected in medical and mental health care settings. The National Institute on Alcohol Abuse and Alcoholism recently released a new guide called "Helping Patients Who Drink Too Much: A Clinician's Guide," which offers guidance for conducting brief interventions and managing patient care. The guide shows physicians how to look for symptoms of alcohol abuse or dependence. The guide is at www.niaaa.nih.gov.

—Mary Ellen Schneider



BRIEF SUMMARY

For Intravenous Use Only

The following is a brief summary only for the management of acute myocardial infarction in adults. Before use, please see full prescribing information.

INDICATIONS AND USAGE

TNKase is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL STUDIES section of full prescribing information).

CONTRAINDICATIONS

TNKase therapy in patients with acute myocardial infarction is contraindicated in the following situations because of an increased risk of bleeding (see WARNINGS):

- Active internal bleeding
- History of cerebrovascular accident
- Intracranial or intraspinal surgery or trauma within 2 months
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension

WARNINGS

Bleeding

The most common complication encountered during TNKase therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention.

Should serious bleeding (not controlled by local pressure) occur, any concomitant heparin or antiplatelet agents should be discontinued immediately.

In clinical studies of TNKase, patients were treated with both aspirin and heparin. Heparin may contribute to the bleeding risks associated with TNKase. The safety of the use of TNKase with other antiplatelet agents has not been adequately studied (see PRECAUTIONS: Drug Interactions). Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with TNKase. Venipunctures should be performed and monitored carefully.

Should an arterial puncture be necessary during the first few hours following TNKase therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with TNKase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of TNKase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP \geq 180 mm Hg and/or diastolic BP \geq 110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects, including those secondary to severe hepatic or renal disease
- Severe hepatic dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (see PRECAUTIONS: Geriatric Use)
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Recent administration of GP IIb/IIIa inhibitors
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute

renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when TNKase is administered.

PRECAUTIONS

General

Standard management of myocardial infarction should be implemented concomitantly with TNKase treatment. Arterial and venous punctures should be minimized. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the noncompressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration

Readministration of plasminogen activators, including TNKase, to patients who have received prior plasminogen activator therapy has not been systematically studied. Three of 487 patients tested for antibody formation to TNKase had a positive antibody titer at 30 days. The data reflect the percentage of patients whose test results were considered positive for antibodies to TNKase in a radioimmunoprecipitation assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TNKase with the incidence of antibodies to other products may be misleading. Although sustained antibody formation in patients receiving one dose of TNKase has not been documented, readministration should be undertaken with caution. If an anaphylactic reaction occurs, appropriate therapy should be administered.

Drug Interactions

Formal interaction studies of TNKase with other drugs have not been performed. Patients studied in clinical trials of TNKase were routinely treated with heparin and aspirin. Anticoagulants (such as heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may increase the risk of bleeding if administered prior to, during, or after TNKase therapy.

Drug/Laboratory Test Interactions

During TNKase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential, mutagenicity, or the effect on fertility.

Pregnancy (Category C)

TNKase has been shown to elicit maternal and embryo toxicity in rabbits given multiple IV administrations. In rabbits administered 0.5, 1.5 and 5.0 mg/kg/day, vaginal hemorrhage resulted in maternal deaths. Subsequent embryonic deaths were secondary to maternal hemorrhage and no fetal anomalies were observed. TNKase does not elicit maternal and embryo toxicity in rabbits following a single IV administration. Thus, in developmental toxicity studies conducted in rabbits, the no observable effect level (NOEL) of a single IV administration of TNKase on maternal or developmental toxicity was 5 mg/kg (approximately 8–10 times the human dose). There are no adequate and well-controlled studies in pregnant women. TNKase should be given to pregnant women only if the potential benefits justify the potential risk to the fetus.

Nursing Mothers

It is not known if TNKase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TNKase is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TNKase in pediatric patients have not been established.

Geriatric Use

Of the patients in ASSENT-2 who received TNKase, 4,958 (59%) were under the age of 65; 2,256 (27%) were between the ages of 65 and 74; and 1,244 (15%) were 75 and over. The 30-day mortality rates by age were 2.5% in patients under the age of 65, 8.5% in patients between the ages of 65 and 74, and 16.2% in patients age 75 and over. The ICH rates were 0.4% in patients under the age of 65, 1.6% in patients between the ages of 65 and 74, and 1.7% in patients age 75 and over. The rates of any stroke were 1.0% in patients under the age of 65, 2.9% in patients between the ages of 65 and 74, and 3.0% in patients age 75 and over. Major bleeding rates, defined as bleeding requiring blood transfusion or leading to hemodynamic compromise, were 3.1% in patients under the age of 65, 6.4% in patients between the ages of 65 and 74, and 7.7% in patients age 75 and over. In elderly patients, the benefits of TNKase on mortality should be carefully weighed against the risk of increased adverse events, including bleeding.

ADVERSE REACTIONS

Bleeding

The most frequent adverse reaction associated with TNKase is bleeding (see WARNINGS).

Should serious bleeding occur, concomitant heparin and antiplatelet therapy should be discontinued. Death or permanent disability can occur in patients who experience stroke or serious bleeding episodes.

For TNKase-treated patients in ASSENT-2, the incidence of intracranial hemorrhage was 0.9% and any stroke was 1.8%. The incidence of all strokes, including intracranial bleeding, increases with increasing age (see PRECAUTIONS: Geriatric Use). In the ASSENT-2 study, the following bleeding events were reported (see Table 1).

Table 1
ASSENT-2
Non-ICH Bleeding Events

	TNKase (n=8461)	Accelerated Activase (n=8488)	Relative Risk for TNKase/Activase (95% CI)
Major bleeding*	4.7%	5.9%	0.78 (0.69, 0.89)
Minor bleeding	21.8%	23.0%	0.94 (0.89, 1.00)
Units of transfused blood			
Any	4.3%	5.5%	0.77
1-2	2.6%	3.2%	(0.67, 0.89)
>2	1.7%	2.2%	

*Major bleeding is defined as bleeding requiring blood transfusion or leading to hemodynamic compromise.

Non-intracranial major bleeding and the need for blood transfusions were lower in patients treated with TNKase.

Types of major bleeding reported in 1% or more of the patients were hematoma (1.7%) and gastrointestinal tract (1%). Types of major bleeding reported in less than 1% of the patients were urinary tract, puncture site (including cardiac catheterization site), retroperitoneal, respiratory tract, and unspecified. Types of minor bleeding reported in 1% or more of the patients were hematoma (12.3%), urinary tract (3.7%), puncture site (including cardiac catheterization site) (3.6%), pharyngeal (3.1%), gastrointestinal tract (1.9%), epistaxis (1.5%), and unspecified (1.3%).

Allergic Reactions

Allergic-type reactions (e.g., anaphylaxis, angioedema, laryngeal edema, rash, and urticaria) have rarely (<1%) been reported in patients treated with TNKase. Anaphylaxis was reported in <0.1% of patients treated with TNKase; however, causality was not established. When such reactions occur, they usually respond to conventional therapy.

Other Adverse Reactions

The following adverse reactions have been reported among patients receiving TNKase in clinical trials. These reactions are frequent sequelae of the underlying disease, and the effect of TNKase on the incidence of these events is unknown.

These events include cardiogenic shock, arrhythmias, atrioventricular block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial ischemia, myocardial reinfarction, myocardial rupture, cardiac tamponade, pericarditis, pericardial effusion, mitral regurgitation, thrombosis, embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Nausea and/or vomiting, hypotension, and fever have also been reported.

DOSAGE AND ADMINISTRATION

Dosage

TNKase is for intravenous administration only. The recommended total dose should not exceed 50 mg and is based upon patient weight.

A single bolus dose should be administered over 5 seconds based on patient weight. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL STUDIES section of full prescribing information).

Dose Information Table

Patient Weight (kg)	TNKase (mg)	Volume TNKase* to be administered (mL)
<60	30	6
60 to <70	35	7
70 to <80	40	8
80 to <90	45	9
\geq 90	50	10

*From one vial of TNKase reconstituted with 10 mL SWFI.

The safety and efficacy of TNKase have only been investigated with concomitant administration of heparin and aspirin as described in the CLINICAL STUDIES section of the full prescribing information.

REFERENCE

1. ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716-22.

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