problem with televancin is that it interferes with certain blood coagulation tests and with a urine dipstick protein test.

The *Medication Guide*'s warnings about NSAID drugs, ACE inhibitors, water pills, and blood thinners, find a counterpart in the *Warnings and Precautions* section of the package insert. The *Warnings and Precautions* warns that "renal adverse event rates were also higher in patients who received concomitant medications known to affect kidney function (e.g., non-steroidal anti-inflammatory drugs, ACE inhibitors, and loop diuretics)" (381).

### h. Warnings in the *Medication Guide* That Correspond to the *Warnings and Precautions* Section of the Package Label

This illustrates how warnings in the *Medication Guide* may be mirrored in the *Warnings and Precautions* section of the package label. This information is from NDA 22465, available on FDA's website at Apr. 2011.

FDA's approval was for *pazopanib* (Votrient®), for the indication of renal cell carcinoma. The FDA reviewer noted that, "the applicant has already specified all the important risks as warnings and precautions in the proposed package label for pazopanib," and further recommended a REMS that included the implementation of a *Medication Guide* and performing postmarketing pharmacoviligance to monitor liver toxicity. FDA stated that the goal of the *Medication Guide* was to, "convey the risks of life-threatening hepatotoxicity, especially the occurrence of severe and fatal hepatotoxicity." In setting forth the requirements for the proposed REMS, FDA stated that the Sponsor:

> will ensure that a Medication Guide is available for distribution to patients with each … pazopanib … prescription in accordance with 21 CFR 208.24 … [and] will include a statement, "Dispense the Medication Guide" … to each patient … on the label of each container … of … pazopanib.

## XVII. EUROPEAN UNION'S RISK MANAGEMENT TOOLS

FDA's REMS finds a counterpart in the RMP of the European Union. The European Union includes various agencies, including *Germany's Federal Institute for Drugs and Medical Devices* (BfArM) and France's *Agence Nationale de Security du Medicament et des Produits de Sante* (ANSM) (382). In the European Union, pharmaceutical companies must submit a *Risk Evaluation and Mitigation Strategy* at the time of application for a marketing authorization. In 2005, EMA introduced the RMP for planning pharmacovigilance and risk management for new drugs. At an earlier time, regulatory authorities had mainly relied on spontaneous reports and industry or investigator-initiated studies (383). In a study of drugs approved by FDA and approved by EMA, Lis et al. (384)

[381]Package insert for, VIBATIV® (telavancin) for injection, for intravenous use; December 2014 (37 pp.). The package insert was acquired from www.vibativ.com on April 7, 2015.

[382]Dowlat HA. The importance and impact of the EU RMP and US REMS to risk–benefit Assessments. Biopractice. Feb. 2011;8 (5 pp.).

[383]Vermeer NS, Duijnhoven RG, Straus SM, et al. Risk management plans as a tool for proactive pharmacovigilance: a cohort study of newly approved drugs in Europe. Clin. Pharmacol. Ther. 2014;96:723–31.

[384]Lis et al. Comparisons of Food and Drug Administration and European Medicines Agency risk management implementation for recent pharmaceutical approvals: report of the International Society for Pharmacoeconomics and outcomes research risk benefit management working group. Value Health 2012;15:1108–18.