c. Black Box Warning

Where a drug presents a serious risk that can lead to death or serious injury, FDA may require that the package insert include a black box warning. This warning informs the physician that patients taking the drug need to be closely monitored (31). Black box warnings include those that require laboratory testing, avoiding other drugs (warning regarding drug–drug interactions), avoiding prescribing in the presence of another specified health condition, or knowing the risks associated with a specific population, such as pregnant women.

Black box warnings take the form of a writing that resides inside a black box. Examples appear below. These examples, which are from drugs discussed earlier in this book, include an anticancer drug (cisplatin), an antiviral drug (ribavirin), and an antidepressant (Zoloft®).

The black box warning for cisplatin (32) is reproduced here:

> **WARNINGS**. Cisplatin injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. Cumulative renal toxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting. Ototoxicity, which may be more pronounced in children, and is manifested by tinnitus, and/or loss of high frequency hearing and occasionally deafness, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteriods, and antihistamines have been effectively employed to alleviate symptoms.
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> **Exercise caution to prevent inadvertent cisplatin overdose**. Doses greater than 100 mg/m^2/cycle once every 3–4 weeks are rarely used. Care must be taken to avoid inadvertent cisplatin overdose due to confusion with carboplatin or prescribing practices that fail to differentiate daily doses from total dose per cycle.

The black box warning for ribavirin (33) reads:

> **WARNING**. COPEGUS (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.
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> Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months

[31]Ricci JR, Coulen C, Berger JE, Moore MC, McQueen A, Jan SA. Prescriber compliance with black box warnings in older adult patients. Am. J. Manag. Care 2009;15:e103–8.

[32]Package insert. Bedford Laboratories, Cisplatin injection, (June 2004).

[33]Package insert. Copegus Roche Laboratories, Inc. (May 2004).