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Important Prescribing Information

Dear Healthcare Provider:

There have been reports of errors in the reconstitution of HERCEPTIN® (Trastuzumab). Improper reconstitution may result in the administration of incorrect doses to patients. We are sending this letter to clarify the instructions for reconstituting HERCEPTIN. **When reconstituting HERCEPTIN, please note the following five precautions:**

1. RECONSTITUTE HERCEPTIN WITH 20 mL of DILUENT
   HERCEPTIN is provided as a sterile, preservative-free lyophilized powder for intravenous (IV) administration along with a 30-mL vial of Bacteriostatic Water for Injection USP, containing 1.1% benzyl alcohol as preservative for reconstituting the product.

   ONLY 20 mL OF BACTERIOSTATIC WATER FOR INJECTION (BWFI), USP, DILUENT SHOULD BE USED TO RECONSTITUTE THE HERCEPTIN VIAL. Use of all 30 mL of diluent results in a lower-than-intended dose of HERCEPTIN. THE REMAINDER (approximately 10 mL) OF THE BWFI DILUENT SHOULD BE DISCARDED.

2. RECONSTITUTE HERCEPTIN WITH PROPER DILUENT
   Care must also be taken to use the packaged BWFI as diluent. The BWFI provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. If, due to a patient's allergy to benzyl alcohol, Sterile Water for Injection without a preservative is used, the reconstituted HERCEPTIN should be used immediately and the unused portion discarded.

3. HANDLE HERCEPTIN CAREFULLY DURING RECONSTITUTION
   Shaking the reconstituted HERCEPTIN or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of HERCEPTIN that can be withdrawn from the vial. Provided below are directions for reconstituting each vial of Trastuzumab.

   a. Using a sterile syringe, slowly inject 20 mL of the BWFI diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.

   b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. DO NOT SHAKE.

   c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

4. EXPECTED HERCEPTIN RECOVERY
   One multi-dose vial of HERCEPTIN reconstituted with 20 mL of the supplied BWFI diluent contains a solution with an approximate concentration of 21 mg/mL of Trastuzumab. The expected recovery is 20 ± 0.5 mL per vial, and can vary depending on the technique applied and the number of withdrawals from the vial.

5. ADMINISTRATION
   HERCEPTIN is to be diluted in saline for IV infusion as described in the enclosed package insert. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

We are working together with the FDA to revise the product labeling accordingly.

Medication errors, either actual or probable, associated with the use of biological products, and any serious adverse events related to such occurrences, can be reported to the FDA via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch Web site at www.fda.gov/medwatch, or by mail (using postage-paid form) at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787.

Please see the enclosed full prescribing information. We hope you find this information useful.

Sincerely,

Susan D. Hellmann, MD, MPH
Senior Vice President
Chief Medical Officer
Genentech, Inc.