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March 9, 2015

IMPORTANT PRESCRIBING AND SAFETY INFORMATION

Subject: **IMPORTANT SAFETY AND INCOMPATIBILTY INFORMATION FOR TREANDA® (bendamustine HCl) INJECTION (45 mg/0.5 mL or 180 mg/2 mL solution)**

Dear Health Care Provider:

TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection).

Do Not Use TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) with Closed System Transfer Devices (CSTDs), Adaptors, and Syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS).

Only use a polypropylene syringe with a metal needle and polypropylene hub to withdraw and transfer TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution). Polypropylene syringes are translucent in appearance.

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) is not compatible with CSTDs, adaptors, and syringes containing polycarbonate or ABS. This incompatibility leads to device failure (e.g., leaking, breaking, or operational failure of CSTD components), possible product contamination, and potential serious adverse health consequences to the practitioner, including skin reactions; or to the patient, including but not limited to, the risk of small blood vessel blockage if they receive product contaminated with dissolved ABS or polycarbonate.

- TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) contains N,N-dimethylacetamide (DMA) which is incompatible with polycarbonate and ABS.
- CSTDs, adaptors, and syringes containing polycarbonate or ABS have been shown to dissolve when they come in contact with DMA.
- Most CSTDs contain either polycarbonate or ABS. **If a CSTD would be used with TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)**, please verify with the CSTD manufacturer or Teva U.S. Medical Information (1-800-896-5855) that the device is compatible for use with TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution).
- **Polycarbonate syringes are clear in appearance. These syringes must not be used.**

Based on discussions with the U.S. Food and Drug Administration, Teva will make the TREANDA for Injection, the lyophilized powder (25 mg/vial or 100 mg/vial) formulation

available so that facilities that use a CSTD or adaptors as supplemental protection during preparation can have access to the product.

Action for Health Care Provider

Selection of TREANDA Formulation to Administer

- TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection). The concentration of bendamustine hydrochloride in TREANDA Injection (solution) is either 45 mg/0.5 mL or 180 mg/2 mL (90 mg/mL) and the concentration of bendamustine hydrochloride in the reconstituted TREANDA for Injection (reconstituted solution of lyophilized powder) is 5 mg/mL.
- DO NOT MIX OR COMBINE THE TWO FORMULATIONS.
- TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) must be withdrawn and transferred for dilution in a biosafety cabinet (BSC) or containment isolator using a polypropylene syringe with a metal needle and a polypropylene hub.
- If a CSTD or adaptor is to be used as supplemental protection during preparation, only use TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder).

Safe Preparation for Intravenous Administration using TREANDA Injection (45 mg/0.5mL or 180 mg/2 mL solution)

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) does not require reconstitution. TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Each vial of TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) is intended for single use only.

Preparation for Intravenous Administration

1. TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) must be diluted in a biosafety cabinet or containment isolator.

2. Aseptically withdraw the volume needed for the required dose from the vial using **a polypropylene syringe with metal needle and polypropylene hub** (e.g., 3 mL BD reference 309657; 5 mL BD reference 309646; or 10 mL BD reference 309604).

3. **Immediately** transfer the contents of the syringe to a 500 mL infusion bag containing 0.9% Sodium Chloride Injection, USP (normal saline) or to a 500 mL infusion bag containing 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The admixture should be a clear colorless to yellow solution.

4. The prepared infusion bag should be inspected visually to ensure the lack of visible particulate matter and discoloration prior to administration.

Safe Preparation for Intravenous Administration using TREANDA for Injection (25mg/vial or 100 mg/vial lyophilized powder)

TREANDA for Injection is a lyophilized powder and must be reconstituted. If a closed system transfer device or adaptor is to be used as supplemental protection during preparation, only use TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder).

1. Aseptically reconstitute each 100 mg TREANDA vial with 20 mL of only Sterile Water for Injection, USP and each 25 mg TREANDA vial with 5 mL of only Sterile Water for Injection, USP. Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. **The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution**. If particulate matter is observed, the reconstituted product should not be used.

2. Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and **immediately** transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless **to slightly yellow solution.**

3. Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. **No other diluents have been shown to be compatible**.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) to Teva Pharmaceuticals at 1-800-896-5855.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You also may contact our medical information department at 1-800-896-5855 if you have any questions about the information contained in this letter or the safe and effective use of TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution).

Sincerely,

Denisa Hurtukova, MD
Vice President, Head of North America Medical Affairs
Teva Pharmaceuticals

Enclosure(s): Full Prescribing Information for TREANDA® (bendamustine HCl) Injection (45 mg/0.5 mL or 180 mg/2 mL solution), TREANDA® (bendamustine HCl) for Injection (25 mg/vial or 100 mg/vial lyophilized powder) Full Prescribing Information