URGENT – THIOTEPA UPDATE

July 25th, 2013

Dear Healthcare Professional,

Due to the current critical shortage of Thiotepa for Injection, USP (Bedford 15 mg/vial; NDC 55390-0030-10) in the United States (US) market, ADIENNE SA is coordinating with the Food and Drug Administration (FDA) to increase the availability of Thiotepa for Injection, USP. In conjunction with the FDA, ADIENNE SA has initiated temporary importation into the US market TEPADINA®, an international (EU) Thiotepa for Injection, USP.

TEPADINA® contains the same active ingredient as the US registered Thiotepa for Injection, USP. However, TEPADINA® is provided in two different size vials, 15 mg/vial and 100 mg/vial. The 15 mg vial contains the same amount of active ingredient as the FDA approved Thiotepa for Injection, USP that has been available in the US market. The 100 mg vial has the same active ingredient as the 15 mg vial, but contains 85 mg more Thiotepa per vial than the 15 mg vial. Both vial sizes of TEPADINA® are a clinically acceptable substitute to the Thiotepa for Injection, USP marketed in the US. The choice of vial size will depend on the dosage required for the specific indication and patient.

There are some key differences in the labeling between the US marketed Thiotepa for Injection, USP, and the European ADIENNE TEPADINA® (please see the comparison table).
In the US, the labeling for Thiotepa for Injection, USP includes: i) treatment of adenocarcinoma of the breast and ovarian cancer; ii) for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities; iii) for the treatment of superficial papillary carcinoma of the urinary bladder; and iv) lymphomas, such as lymphosarcoma and Hodgkin's disease. The label in EU is for the use as part of conditioning therapy prior to autologous or allogeneic hematopoietic progenitor cell transplantation for the treatment of malignant and non-malignant disease. In the US package insert, the recommended dose of Thiotepa for the indications listed for intravenous use is 0.3 to 0.4mg/kg and the recommended dose of Thiotepa for intravesical instillation in the US package insert is 0.6 to 0.8mg/ml. **These doses are less than one tenth of the TEPADINA® dose recommended for conditioning therapy in the EU label that accompanies TEPADINA®.** Please refer to the TEPADINA® package insert for more information. TEPADINA® can be safely substituted for any indication that you are currently using the FDA approved Thiotepa for Injection, USP. **Please be sure that you prescribe proper dose for the indication.** The label for TEPADINA® 15 mg/vial and TEPADINA® 100 mg/vial are identical except for the amount of Thiotepa for Injection in the vial -15 mg versus 100 mg respectively. Do not use the trade name when ordering the drug in the US. Please use Thiotepa for Injection, USP.

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The Thiotepa in TEPADINA® 15 mg/vial and 100 mg/vial is manufactured at IDT Australia Limited with an active Drug Master File on file with the FDA. The facility that manufactures Thiotepa for TEPADINA is in compliance with FDA current good manufacturing practices.

The packaging for TEPADINA® differs from the FDA approved labeling for Thiotepa for Injection, USP supplied by Bedford. TEPADINA® has no bar code or NDC number. Additionally, the box label will be in English plus two other languages (either French and German or Spanish and Italian). The label on the vial and the package insert is in English.

To order TEPADINA®, please contact Customer Service: Guglielmo Bianchi by phone **+41.789.451.694**, fax **+ 41.919.211.978** or e-mail **guglielmo.bianchi@adienne.ch**. Because the drug will be shipped from Switzerland by a specialized courier with a temperature controlled container (+2 to +8ºC), shipments will only be made on Monday, Tuesday and Friday.
If TEPADINA® is required urgently; ADIENNE SA will do everything possible to meet the needs of clinical team. TEPADINA® should be handled exactly as you have handled the FDA approved Thiotepa for Injection, USP. Once received TEPADINA® vials should be stored between +2 and +8ºC, once reconstituted; and the reconstituted drug should be used within 8 hours.

To report adverse events or medication errors among patients administered TEPADINA®, please contact Pharmacovigilance: Dr. Daniela Rota by FAX: +**39.02.957.421.72**, e-mail: **safety@adienne.com** or Mobile: **+39.334.90.57.688**. ADIENNE will ensure that the FDA is aware of any adverse event. Adverse events that may be related to the use of this product may also be reported using the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail or by fax:

- Online: www.fda.gov/medwatch/report.htm
- Regular Mail: use postage-paid FDA form 3500 available at www.fda.gov/MedWatch/getforms.htm. Mail to: MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: +1-800-FDA-0178

At this time, no other entity except ADIENNE SA is authorized by the FDA to import or distribute TEPADINA® (thiotepa for injection 15mg and 100mg vials) in the United States. Any sale of TEPADINA® 15mg or 100mg vials from any entity other than ADIENNE SA. will be considered a violation of the Federal Food, Drug and Cosmetic Act and will be subject to enforcement by FDA.

Thank you,

Joseph O'Neill, General Manager for North America, ADIENNE SA