CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: December 1, 2016
From: Natalie Simpson, PhD
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology Oncology Products (OHOP)
Re: Labeling Review
NDA: 208264
Drug: TEPADINA (thiotepa)
Indication: To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor cell transplantation for patients with class 3 β-thalassemia; for treatment of adenocarcinoma of the breast or ovary; for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities; and, for treatment of superficial papillary carcinoma of the urinary bladder.
Applicant: ADIENNE SA

TEPADINA (thiotepa) is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethyleneimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principle bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines. The Applicant submitted this 505 (b)(2) NDA in March of 2016, relying on the nonclinical data reviewed for initial approval of thiotepa under and NDA 11683 (FDA approved in 1959), the reference listed drug (RLD) THIOPLEX (FDA approved in 1994), and the ANDA 75547 label. Published articles were also submitted in support of the use of the drug for the proposed indication and for toxicities associated with the drug.

The labeling for NDA 208264 was made consistent with nonclinical information from the only available thiotepa label (ANDA 75547[1]), including updating sections (5, 8, 13 and use in specific populations) to fit the PLLR format. Specific PLLR compliant language was derived mainly from the HYDREA and ADCETRIS labels to establish consistent language among products with comparable severities of nonclinical toxicities.[2,3] The Applicant proposed changes in wording of the nonclinical information of the TEPADINA label that were inconsistent with the ANDA 75547 label. (b) (4) (b) (4) These changes were not acceptable and excluded from the TEPADINA label.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/075547Orig1s006lbl.pdf
[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/016295Orig1s047,s048Lbl.pdf
[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125388s084lbl.pdf

(b) (4)

While the Applicant did not propose adding new animal safety data to the label, the Applicant submitted published references describing neurotoxicity/degenerative effects and impaired neurogenesis with cognitive effects in animals treated with thiotepa.[6,7,8,9] The review team concluded that these animal safety findings, discovered after the approval of the RLD, did not need to be added to the TEPADINA label since comparable adverse effects have been observed in humans and are commonly observed with cytotoxic agents.

[6] Rzeski, W et al, 2004, Anticancer agents are potent neurotoxins in vitro and in vivo, Ann Neurol, 56:351-360.
[7] Mondie, CM et al, 2010, The chemotherapy agent, thiotepa, yields long-term impairment of hippocampal cell proliferation and memory deficits but not depression-related behaviors in mice, Behav Brain Res, 209(1):66-72.
[8] Mignone, RG et al, 2006, Potent inhibition of cell proliferation in the hippocampal dentate gyrus of mice by the chemotherapeutic drug thiotepa, Brain Research, 1111(1):26-29.
[9] Wilson, CL et al, 2013, Chemotherapy drug thiotepa exacerbates stress-induced anhedonia and corticosteroid responses but not impairment of hippocampal cell proliferation in adult mice, Behav Brain Res, 236(1):180-185.

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/s/

NATALIE E SIMPSON
12/28/2016

CHRISTOPHER M SHETH
12/28/2016
I concur