CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-684 / S-045
50-750 / S-012

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

NDA#	50-684 (SCF-045), 50-750 (SCF-012)
PRODUCT	Piperacillin sodium/Tazobactam sodium (Zosyn®)
FORMULATION	Sterile powder for injection
SUBMISSION DATE	May 27, 2005
SUBMISSION TYPE	Labeling Supplement
SPONSOR	Wyeth Pharmaceuticals, Philadelphia, PA 19101-8299
REVIEWER	Charles R. Bonapace, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

Prior Approval Labeling Supplement

Wyeth submitted prior approval labeling supplements for piperacillin sodium/tazobactam sodium (Zosyn®) sterile powder for injection (NDA 50-684) and piperacillin sodium/tazobactam sodium (Zosyn®) Galaxy containers (NDA 50-750) to change the formulation with the objective of ensuring compliance with the USP <788> specifications for sub-visible particulates in intravenous (IV) drug products. The current compendial limits for particulates in USP <788> specifications are tighter than previous limits when piperacillin sodium/tazobactam sodium was originally approved on October 22, 1993. The reformulated piperacillin sodium/tazobactam sodium provides increased assurance of product quality by reducing the level of sub-visible particulates to a level meeting the tighter USP <788> specifications. Additionally, the sponsor believes that the reformulated piperacillin sodium/tazobactam sodium provides for co-administration with certain aminoglycosides (amikacin, gentamicin, and tobramycin) and dilution with Lactated Ringers Injection which is prohibited with the currently marketed formulation.

The reformulated piperacillin sodium/tazobactam sodium contains two additional excipients, edetate disodium dihydrate (EDTA) as a metal chelator and citric acid monohydrate as a buffer. The citric acid monohydrate forms sodium citrate in situ. Both EDTA and citric acid are associated with inhibiting particulate formation. As a metal chelator, EDTA reduces the availability of metal ions such as zinc which contribute to the formation of aggregates (dimerization of piperacillin and/or adducts with aminoglycosides). The buffering effect of citric acid improves the ability of piperacillin sodium/ tazobactam sodium lyophile or solution to remain within an optimum pH range at which piperacillin sodium is the most soluble and stable, thus avoiding formation of less soluble piperacillin acid and particulates.

This review will focus on the results of Y-site compatibility studies with reformulated piperacillin/ tazobactam vials and Galaxy containers and the aminoglycosides amikacin, tobramycin and gentamicin. The review of study reports RPT-58383 and RPT-59087 can be found in Appendix A.

Based on the results of the compatibility studies (RPT-58383 and RPT-58383), the sponsor's and reviewer's proposed changes for piperacillin/tazobactam vials (NDA 50-684) and Galaxy containers (NDA-750) are shown below:

WITHHOLD 6 PAGE(S)

Draft labeling

RECOMMENDATIONS:
This submission was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Venkat R. Jarugula, Ph.D. _____
Team Leader

cc:
Division File: NDA 50-684 (SCF-045), 50-750 (SCF-012)
HFD-520 (CSO/Samanta)
HFD-520 (MO/Alexander)
HFD-520 (CMC/Vidra, Sloan)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm./Biopharm.)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Bonapace
9/29/2005 11:26:55 AM
BIOPHARMACEUTICS

Venkateswar Jarugula
9/30/2005 10:31:57 AM
BIOPHARMACEUTICS