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SANDOZ

March 1, 2006

OVERNIGHT MAIL

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

RE: Supplement - Docket No. 2005P-0456/CP1
Piperacillin and Tazobactam for Injection

Dear Sir/Madam:

Sandoz Inc. hereby supplements the above-identified Citizen Petition, docketed on November 8, 2005, as follows.

As noted in our citizen petition, the Reference Listed Drug, Zosyn® (piperacillin and tazobactam for injection), the subject of NDA 50-684, held by Wyeth Pharmaceuticals Inc. was first approved October 22, 1993. The product was supplied in a conventional vial and ADD-Vantage vial containing 2.25 g, 3.375 g and 4.5 g of piperacillin sodium and tazobactam sodium, equivalent to 2 grams of piperacillin and 0.25 g of tazobactam, 3 grams of piperacillin and 0.375 g of tazobactam, 4 grams of piperacillin and 0.5 g of tazobactam per vial.

On September 30, 2005, FDA approved a reformulation of the drug product and labeling changes for Zosyn® (piperacillin and tazobactam for injection), under the subject NDA 50-684, Supplement Number 045. In this supplement, Wyeth Pharmaceuticals Inc. added edetate disodium dehydrate, which acts as a metal-chelating agent, and citric acid, which acts as a buffer.

In our citizen petition, we requested the Commissioner of Food and Drugs to make a determination that the discontinued formulation (without edetate disodium and citric acid) of the Reference Listed Drug, Zosyn® (piperacillin and tazobactam for injection), the subject of NDA 50-684, held by Wyeth Pharmaceuticals Inc., is suitable for an Abbrevaited New Drug Appliication and that the product was not discontinued for safety and efficacy reasons.

2005P-0456 SUP 1

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To support our request, we would like to inform you that scientific literature clearly indicates that piperacillin and tazobactam, without edentate disodium and citric acid (i.e. sodium citrate), is stable in solutions for infusion. No scientific data or published clinical experience indicates a problem with the stability of piperacillin and tazobactam under routine clinical conditions.

Moreover, the stability of piperacillin and tazobactam under clinical conditions has been shown to be comparable or higher than for other β-lactam antibiotics suitable for parenteral use[i]. Reference the following tables which show the stability of β-lactams in water at 37°C over time at the maximum concentration tested.

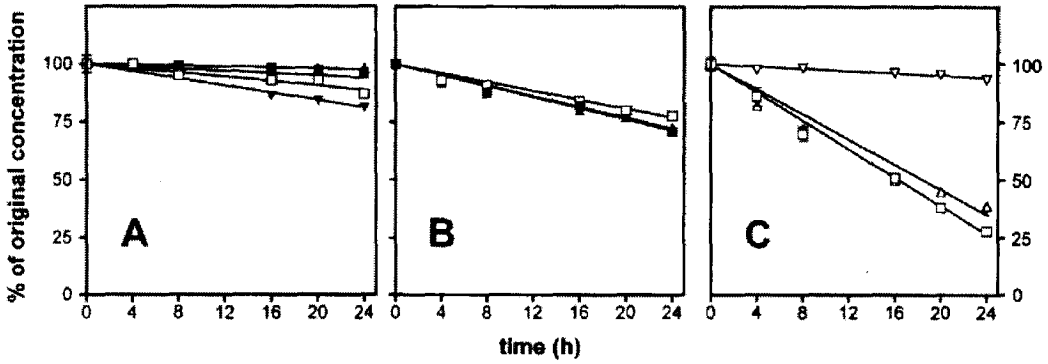

FIG. 1. Stability of the β-lactams in water at 37°C over time at the maximum concentration tested. (A) Symbols: △, 10% aztreonam; □, 12.8% piperacillin; ■, 12.8% piperacillin plus tazobactam (since the slope for 12.8% azocillin was almost identical to that for piperacillin-tazobactam, it was omitted for the sake of clarity); ▼ 12.8% mezlocillin. (B) Symbols: ■, 12% ceftazidime; □, 5% cefepime; ▲, 3.2% cefpirome. (C) Symbols: □, 0.8% imipenem plus cilastatin; △, 6.4% meropenem; ▽, 6.4% faropenem. All values are the means of three independent determinations ± the standard deviation (SD; symbols without bars indicate values for which the SD is smaller than the symbol size).

Time during which β-lactams remain >90% stable[i]

Drug(s)	Time (h, min)[a] at:	
	37°C	25°C
Aztreonam	>24	ND
Piperacillin	21, 40	~30
Piperacillin + tazobactam	>24	⩾72[b]
Azlocillin	>24	⩾72[b]
Mezlocillin	14	46, 30
Ceftazidime	8	24
Cefepime	13	20, 30
Cefpirome	7, 15	23, 40
Imipenem + cilastatin	2, 45	3, 30
Meropenem	1, 50	5, 15
Faropenem	>24	~80

[a] Decays were monitored for 24 h; the slope was calculated by linear regression and used to determine the 90% stability time point. All data were rounded to the closest 15-min value. ND, not determined.

[b] 90% stability for at least 72 h, but the slope was too weak to calculate the 90% intercept value with accuracy from the 24-h decay data.

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Even at storage temperatures as high as 37°C the stability of piperacillin and tazobactam in solution has been found to be high enough for virtually all clinical applications. In these experiments no precipitations were observed under any storage conditions of the solution tested, i.e. at 4°C, 23°C or 37°C.[ii]

These findings have been recently confirmed for solutions of piperacillin and tazobactam in buffered/unbuffered 0.9% sodium chloride solution using different primary packaging materials, i.e. PVC and non-PVC polymer bags. Under the most stable conditions, i.e. buffered saline stored in non-PVC bags, the solution of piperacillin and tazobactam was stable at room temperature and day light for as long as 7 days. With protection from daylight, the solution was stable for 10 days at room temperature and for 58 days at 7°C. However, even under the most "unstable" conditions tested, i.e. solution in unbuffered saline stored in PVC bags, the solution was found to be stable for 4 days at room temperature (with or without daylight) and for 5 days at 7°C.[iii] These data indicate sufficient stability of conventional piperacillin and tazobactam preparations without addition of EDTA (edetate disodium dehydrate) and sodium citrate.

Additonally, Wyeth Pharmaceuticals announced, in December 1, 2005, that the re-formulation did not affect the dosing, safety profile, and efficacy of ZOSYN. Refer to the "Dear Health Care Provider" letter in Attachment 1 where Wyeth makes this announcement to the public.

Accordingly, Sandoz Inc. believes that the information presented in this supplement to the Citizen Petition, docket number 2005P-0456/CP1, supports the fact that the product stability is not affected by the addition of EDTA (edetate disodium dehydrate) and sodium citrate.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

If you have any questions or need additional information, please feel free to contact me.

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Regulatory Affairs

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/jep/lah

Enclosure: Attachment 1

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[i] Viaene E, Chanteux H, Servais H, Mingeot-Leclercq M-P, Tulkens PM. Comparative stability studies of antipseudomonal β-lactams for potential administration through portable elastoeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother 2002; 46: 2327-32.

[ii] Park T, Le-Bui LPK, Chung KC, Rho JP, Gill MA. Stability of piperacillin sodium-tazobactam sodium in peritoneal dialysis solutions. Am J Health-Syst Pharm 1995; 52: 2022-4.

[iii] Rigge DC, Jones MF. Shelf lives of aseptically prepared medicines – Stability of piperacillin/tazobactam in PVC and non-PVC bags. J Pharma Biomed Anal 2005; 39: 339-43.

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Attachment 1

Copy of Wyeth's Dear Health Care Provider Letter

Wyeth Pharmaceuticals
500 Arcola Road
Collegeville, PA 19426

Wyeth®

December 1, 2005

Dear Health Care Provider:

We're pleased to announce that the FDA has approved a new formulation of ZOSYN® (piperacillin/tazobactam) that has an expanded compatibility profile.

Reformulated ZOSYN in Standard, ADD-Vantage®, and Pharmacy Bulk Vials includes 2 new components:

- EDTA (edetate disodium dihydrate), which acts as a metal-chelating agent
- Sodium citrate, which acts as a buffer

Reformulated ZOSYN in Galaxy® Bags includes 1 new component, EDTA. Sodium citrate has always been an ingredient of ZOSYN in Galaxy Bags.

The formulation changes resulted in compatibility with Lactated Ringer's Solution (LRS) and certain aminoglycosides.

ZOSYN–Same Name. Expanded Compatibility.

- Reformulated ZOSYN is compatible with LRS for dilution
- As shown in the Compatibility Information listed below, when necessary, reformulated ZOSYN can be administered simultaneously with either amikacin or gentamicin, via Y-site infusion at certain doses and certain concentrations, and with certain diluents

The dosing, safety profile, and efficacy of ZOSYN have not changed. You may administer reformulated ZOSYN as you have been doing with the former ZOSYN formulation not containing EDTA. **However, you should note that the former ZOSYN formulation not containing EDTA is NOT compatible with LRS or with aminoglycosides for Y-site infusion. You must be aware of this incompatibility if you are using the former ZOSYN formulation not containing EDTA.**

Compatibility Information for Reformulated ZOSYN in Standard, ADD-Vantage, and Pharmacy Bulk Vials Only

Due to the *in vitro* inactivation of aminoglycosides by β-lactam antibiotics, ZOSYN and aminoglycosides are recommended for separate administration. However, in circumstances where coadministration via Y-site is necessary, reformulated ZOSYN containing EDTA supplied in single-dose vials or pharmacy bulk vials is compatible for simultaneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	ZOSYN dose (g)	ZOSYN diluent volume (mL)	Aminoglycoside concentration range* (mg/mL)	Acceptable diluents
Amikacin	**2.25, 3.375, 4.5**	**50, 100, 150**	**1.75-7.5**	**0.9% sodium chloride or 5% dextrose**
Gentamicin	**2.25, 3.375, 4.5**	**100, 150**	**0.7-3.32**	**0.9% sodium chloride**

*The concentration ranges in this table are based on administration of the aminoglycoside in divided doses (10-15 mg/kg/day in 2 daily doses for amikacin and 3-5 mg/kg/day in 3 daily doses for gentamicin). Administration of amikacin or gentamicin in a single daily dose or in doses exceeding those stated above via Y-site with ZOSYN containing EDTA has not been evaluated. See full prescribing information for each aminoglycoside for complete dosage and administration instructions.

Compatibility Information for Reformulated ZOSYN* in Galaxy Bags Only

Due to the *in vitro* inactivation of aminoglycosides by β-lactam antibiotics, ZOSYN and aminoglycosides are recommended for separate administration. However, in circumstances where coadministration via Y-site is necessary, reformulated ZOSYN containing EDTA supplied in Galaxy Bags is compatible for simultaneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	ZOSYN dose (g)	Aminoglycoside concentration range* (mg/mL)	Acceptable diluents
Amikacin	**2.25, 3.375, 4.5**	**1.75-7.5**	**0.9% sodium chloride or 5% dextrose**
Gentamicin	**2.25 or 4.5**	**0.7-3.32**	**0.9% sodium chloride**

*The concentration ranges in this table are based on administration of the aminoglycoside in divided doses (10-15 mg/kg/day in 2 daily doses for amikacin and 3-5 mg/kg/day in 3 daily doses for gentamicin). Administration of amikacin or gentamicin in a single daily dose or in doses exceeding those stated above via Y-site with ZOSYN containing EDTA has not been evaluated. See full prescribing information for each aminoglycoside for complete dosage and administration instructions.

- ZOSYN Galaxy Bags are available as 2.25 g per 50 mL, 3.375 g per 50 mL, and 4.5 g per 100 mL
- ZOSYN 3.375 g per 50 mL Galaxy Bags are NOT compatible with gentamicin for coadministration via a Y-site due to higher concentrations of piperacillin and tazobactam
- **ZOSYN is not compatible with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of ZOSYN with other aminoglycosides has not been established. Only the concentration and diluents for amikacin or gentamicin with the dosages of ZOSYN listed above have been established as compatible for coadministration via Y-site infusion. Simultaneous coadministration via Y-site infusion in any manner other than listed above may result in inactivation of the aminoglycoside by ZOSYN.**

New NDC Codes for Ordering Reformulated ZOSYN

There are 10 new NDC codes, as shown in the following table:

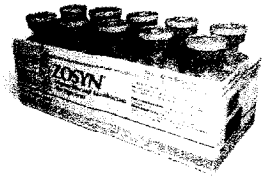
ZOSYN Dosage	Single-dose Vial (10 per box)	ADD-Vantage Vial (10 per box)	Galaxy Bag* (24 per box for 2.25 g and 3.375 g; 12 per box for 4.5 g)	Pharmacy Bulk Vial Package†
2.25 g	NDC 0206-8852-16	NDC 0206-8852-18	NDC 0206-8860-02	
3.375 g	NDC 0206-8854-16	NDC 0206-8854-18	NDC 0206-8861-02	
4.5 g	NDC 0206-8855-16	NDC 0206-8855-18	NDC 0206-8862-02	
40.5 g (supplied as a powder)				NDC 0206-8859-10

*ZOSYN in Galaxy Bags is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in single-dose plastic containers.

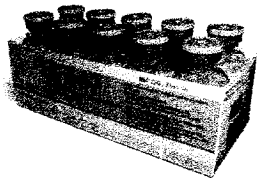
†ZOSYN in Pharmacy Bulk Vial Packages is supplied as a powder for reconstitution.

New ZOSYN® Packaging

Changes have also been made to the packaging, to differentiate between current ZOSYN and reformulated ZOSYN.



Current Tray



Reformulated ZOSYN Tray

- The panels on the trays of vials have a yellow background and include the language "contains...edetate disodium dihydrate" beneath the NDC code

Current Standard Vial

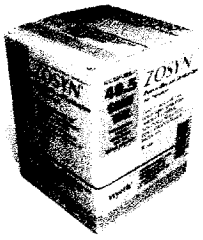
Reformulated ZOSYN Standard Vial

- Labels on individual standard vials have a yellow background behind the ZOSYN logo

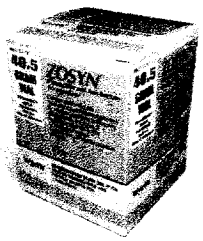
Current ADD-Vantage® Vial

Reformulated ZOSYN ADD-Vantage® Vial

- Labels on individual ADD-Vantage® vials have a yellow background behind the ZOSYN logo

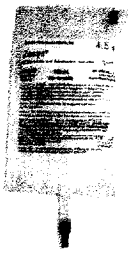


Current Pharmacy Bulk Vial Package



Reformulated ZOSYN Pharmacy Bulk Vial Package

- On the pharmacy bulk vial package, the panels have a yellow background and include the language "contains 9 mg of edetate disodium dihydrate" in the description beneath the logo



Current Galaxy® Bag

Reformulated ZOSYN Galaxy® Bag

- The Galaxy® Bag has a red background with ZOSYN and the generic in white type and includes the language "contains...Edetate Disodium Dihydrate added as a metal chelator" in the description

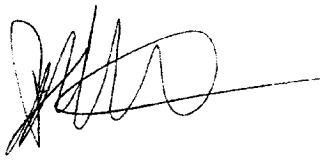
For further information...

For further information about reformulated ZOSYN, please refer to the enclosed package inserts:

- ZOSYN in Standard and ADD-Vantage vials; and
- ZOSYN in Galaxy Bags, which is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in single-dose plastic (PL 2040 Plastic) containers

You can also contact your Wyeth representative, or call 1-800-395-9938. For your information, the current formulation of ZOSYN will be phased out with the release of reformulated ZOSYN.

Sincerely,



Brian Andresen, Product Director
Wyeth Pharmaceuticals