PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zevtera® 500 mg powder for concentrate for solution for infusion (ceftobiprole)

This is a summary of the Risk Management Plan (RMP) for Zevtera. The RMP details important risks of Zevtera, how these risks can be minimised, and how more information will be obtained about Zevtera's risks and uncertainties (missing information).

Zevtera's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Zevtera should be used.

VI.I. The medicine and what it is used for

Zevtera is authorised for the treatment of the following infections in adults:

- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
- Community-acquired pneumonia (CAP)

It contains ceftobiprole medocaril as the active substance and it is given by intravenous infusion.

VI.II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zevtera, together with measures to minimise such risks and the proposed studies for learning more about Zevtera's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Zevtera these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Zevtera is not yet available, it is listed under ‘missing information’ below.

VI.II.A List of important risks and missing information

Important risks of Zevtera are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zevtera. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Hepatic enzymes elevated • Hyponatraemia • Hypersensitivity reactions , including anaphylactic reactions • Pseudomembranous colitis / *Clostridium difficile* colitis • Convulsions • Renal toxicity (including potential interactions with nephrotoxic drugs) • Precipitation of infusion solutions when mixed with calcium-containing solutions
Important potential risks	• Development of drug-resistant bacteria • Off-label use in children and adults • Haemolytic anaemia / Coombs test • Interaction with copper reduction technique to measure urine glucose • Interaction with Jaffé method to measure creatinine • Cytochrome P450 (CYP) drug interactions
Missing information	• Pregnancy and lactation • Paediatric subjects • Use in patients with hepatic impairment • Use in human immunodeficiency virus (HIV) positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression • Safety data in patients with end-stage renal failure

VI.II.B Summary of important risks

Important identified risks:

Important identified risk: HEPATIC ENZYME ELEVATIONS	
Evidence for linking the risk to the medicine	• Scientific literature: transient elevations in hepatic enzymes in patients receiving cephalosporins at therapeutic serum levels (Thompson 2003, Fekety 1990, Meyers 1985, Platt 1982, Smith 1982); • Clinical trials: frequency of increased hepatic enzymes was similar with the active comparator of the same therapeutic class: 6.3% for ceftobiprole-treated subjects and 5.9% for comparator-treated subjects.
Risk factors and risk groups	In general, risk factors for elevations in hepatic enzymes (Ioannou 2006) include: • obesity and increased waist-to-hip ratio (Samadi 2007) • age > 60 years • chronic hepatitis infections (hepatitis B, C) • alcohol ingestion • in critically ill patients, sepsis, shock, hyperalimentation • concomitant use of several medications (Reddy 1995)
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: HYPONATRAEMIA	
Evidence for linking the risk to the medicine	• Established risk of intravenous administration of medication in a large volume, which dilutes the patient's serum and decreases the concentration of sodium in serum, resulting in hyponatraemia. • Clinical trials: the incidence of hyponatraemia in the ceftobiprole group was slightly higher to the one in the comparator group, 6.0% and 4.7%, respectively. This data suggests that the differences may occur more by chance than by any intrinsic mechanism associated with administration of the drug.

Important identified risk: HYPONATRAEMIA	
Risk factors and risk groups	Risk factors: • congestive heart failure • renal failure • hepatic impairment • Central nervous system (CNS) injury • chronic or acute lung disease • cancer • age (elderly patients) • concomitant use of diuretics.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: HYPERSENSITIVITY REACTIONS, INCLUDING ANAPHYLACTIC REACTIONS	
Evidence for linking the risk to the medicine	• Scientific literature: serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactam antibiotics (e.g., of cephalosporin class) (Kemp 2002, Kelkar 2001, Gruchalla 2003). • Non-clinical trials: histaminergic reactions to ceftobiprole were observed in dogs. • Clinical trials: the incidence of hypersensitivity was slightly higher in ceftobiprole group than in comparator group, 5.5% and 4.5%, respectively. There was one serious and one non-serous case of anaphylaxis following ceftobiprole administration.
Risk factors and risk groups	Serious hypersensitivity reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. The greatest risk factor for anaphylactic reaction to cephalosporins is a history of allergy to penicillin and other cephalosporins. The risk for anaphylactic reaction can be increased (by a factor of about 3) for patients with known hypersensitivity to penicillin. Patients with a prior reaction to cephalosporin may be at increased risk for future reactions (Kemp 2002).
Risk minimisation measures	Routine risk minimisation measures:

Important identified risk: HYPERSENSITIVITY REACTIONS, INCLUDING ANAPHYLACTIC REACTIONS	
	• SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: PSEUDOMEMBRANOUS COLITIS / *Clostridium difficile* COLITIS	
Evidence for linking the risk to the medicine	• Scientific literature: pseudomembranous colitis /*Clostridium difficile* colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. (Gerding 1995, Barlett 2005, Hirschorn 1994, Schroeder 2005). • Clinical trials: there were 6 (0.9%) reports of pseudomembranous colitis / *Clostridium difficile* colitis in the ceftobiprole group and 6 (0.8%) reports in the comparator groups.
Risk factors and risk groups	Major predisposing factors include: • antibiotic therapy • advanced age • number and severity of underlying diseases • faulty immune response to *Clostridium difficile* toxins (Schroeder 2005) Patients at highest risk for fulminant disease include those who recently received immunosuppressive therapy or recently under-went surgical procedures and those patients with a previous history of *Clostridium difficile*-associated diarrhoea (Schroeder 2005).
Risk minimisation measures	outine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: CONVULSIONS	
Evidence for linking the risk to the medicine	• Scientific literature/ established risk: convulsions and other adverse central nervous system (CNS) experiences have been reported during treatment with cephalosporins (Calandra 1988). • Clinical trials: there were 15 (2.2%) reports involving convulsions in the ceftobiprole group, compared to 6 (0.8%) in the comparator group. Most of the patients had had a history of head trauma/injury or a CNS abnormality that may have predisposed them to convulsions.

	• Post-marketing data: five reports of convulsions have been identified during post-marketing experience. 2 of 5 patients had known risk factors for convulsions, such as atypical cerebral bleeding and renal insufficiency.
Risk factors and risk groups	During treatment with cephalosporins, convulsions have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of convulsions) or with bacterial meningitis and/or compromised renal function (Calandra 1988, Wallace 1997, Schliamser 1991, Ruffmann 2006). Patients at highest risk for beta-lactam-induced convulsions include those: • with impaired renal function • infants • elderly • with meningitis • undergoing intraventricular antibiotic therapy • with a history of convulsions Additional risk factors include: • other drugs that lower the convulsions threshold, e.g., theophylline synergistic effect of cyclosporin
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4, 4.8 and 5.3 • PL sections 2 and 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: : RENAL TOXICITY (including potential interactions with nephrotoxic drugs)	
Evidence for linking the risk to the medicine	• Non-clinical trials: high doses of ceftobiprole were associated with mortality due to acute renal failure. At these doses there was precipitation of drug-like material in the renal tubules leading to renal tissue damage, which was partly reversible in the 4 week recovery period. • Clinical trials: – Phase 1: one patient developed acute renal failure following ceftobiprole and vancomycin administration after hip surgery. – Phase 3 CAP study: the incidence of renal and urinary adverse events (AEs) was lower in ceftobiprole group than in comparator group, 1% and 2.8%, respectively. – Phase 3 HAP study: the incidence of renal and urinar AEs was higher in subjects receiving ceftobiprole than in those receiving comparator, 8.5% and 5.7% respectively. • Post-marketing data: two reports of renal toxicity have been identified cumulatively (one with fatal outcome).

Important identified risk: : RENAL TOXICITY (including potential interactions with nephrotoxic drugs)	
Risk factors and risk groups	There are a number of well known risk factors for acute renal failure or renal impairment: • Sepsis and serious infections are themselves major risk factors. Superinfection amplifies the risk • Comorbidities: elderly, chronic kidney disease, heart failure, atherosclerotic peripheral vascular disease, liver disease, diabetes and obesity. • Concomitant nephrotoxic medications, e.g., aminoglycoside antibiotics, loop diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) , angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, contrast media • Inadequate renal perfusion, e.g., due to failure to detect or correct dehydration. In CAP/HAP subjects it can be difficult to identify the cause of any deteriorating renal function. In general the risk of developing treatment emergent renal events in CAP (1%) was similar to that for subjects with complicated skin and soft tissue infections (cSSTI) (2.1%). Unsurprisingly subjects with HAP had a higher rate of renal adverse events (AEs) with 8.5% reported although the risk was no greater in VAP.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4, 4.8, 5.2 and 5.3 • PL sections 2, 3 and 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important identified risk: PRECIPITATION OF INFUSION SOLUTIONS WHEN MIXED WITH CALCIUM-CONTAINING INFUSIONS	
Evidence for linking the risk to the medicine	• *In-vitro* experiments: laboratory findings proved the incompatibility between ceftobiprole medocaril and calcium containing infusions. Ceftobiprole medocaril is incompatible with calcium-containing solutions with higher concentrations of calcium salts, such as parenteral nutrition mixtures (0.735 mg/mL), and calcium chloride solutions (40 mg/mL). Precipitates can only be formed *ex vivo*
Risk factors and risk groups	Patients who would receive calcium-containing solutions and ceftobiprole medocaril in the same intravenous line.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 6.2 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None

Important potential risks:

Important potential risk: DEVELOPMENT OF DRUG-RESISTANT BACTERIA	
Evidence for linking the risk to the medicine	• Scientific literature: Selection of resistant bacteria, especially *Enterobacteriaceae* and *Pseudomonas aeruginosa* known to develop resistance after cephalosporin therapy (Chow 1991, Kaye 2001). Most resistance that will be expected with ceftobiprole involves beta-lactamase-mediated mechanisms due to the hydrolysis of ceftobiprole by these enzymes. In studies that identified bacteremic patients with extended spectrum beta-lactamase (ESBL)-producing *K. pneumoniae*, mortality rates were 24% within 14 days of detection (Paterson 2004). • Clinical trials: Few cases of ceftobiprole resistant Gram-negative bacteria were observed in clinical trials. Resistance was either due to increased expression of AmpC cephalosporinase or to expression of ESBLs. The number of ESBL positive *Enterobacteriacea* has been increasing in recent years and infections with those organisms are generally associated with a worse outcome.
Risk factors and risk groups	Prior therapy with other beta-lactams, especially cephalosporins or beta-lactamase inhibitor combinations. Prior hospitalisation or nursing home resident (Kaye 2001).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 5.1 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • BSAC Respiratory Resistance Surveillance Programme • BSAC Bacteraemia Resistance Surveillance Programme • IHMA-2197 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: OFF-LABEL USE IN ADULTS AND CHILDREN	
Evidence for linking the risk to the medicine	• Approved indication: HAP (excluding VAP) and CAP treatment in patients over 18 years of age. • Existence of potential for ceftobiprole (Zevtera) to be used off-label for the treatment of patients with VAP, and for other acute infections such as bone infections, and cSSTIs. Also, the potential for off-label use of ceftobiprole in the paediatric and adolescent population is acknowledged. • Post-marketing data: 9 reports of ceftobiprole use for off-label various infections in adults were received. Aditionally, one off-label use was reported for unknown indication. No cases of off-label use in patients younger than 18 years were reported.

Important potential risk: OFF-LABEL USE IN ADULTS AND CHILDREN	
Risk factors and risk groups	Risk groups: children with CAP or HAP, patients with VAP and other acute infections such as bone infections and cSSTIs
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 4.4 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (BPR-PAS-001) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: HAEMOLYTIC ANAEMIA / COOMBS TEST	
Evidence for linking the risk to the medicine	• Scientific literature: Haemolytic anaemia is a known risk for cephalosporine antibiotics (Garratty 2010). • Clinical trials: no evidence of haemolytic anaemia, however, the possibility that haemolytic anaemia may occur in association with ceftobiprole treatment cannot be ruled out.
Risk factors and risk groups	No specific risk factor has been identified for drug-induced autoimmune haemolytic anaemia.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • Legal status: administration by physician Additional risk minimisation measures: • None

Important potential risk: INTERACTION WITH WITH COPPER REDUCTION TECHNIQUE TO MEASURE URINE GLUCOSE	
Evidence for linking the risk to the medicine	• Scientific literature: Literature data indicate that some cephalosporins (including cefotaxime, cefotoxim and cefamandole) may interact with the copper reduction technique used for the measurement of urine glucose, inducing false positive reactions (McManus 1983). This interaction does not occur with enzyme-based tests for glucosuria. • Clinical trials: Interactions between ceftobiprole and copper reduction tests of glucosuria were not investigated in clinical studies.
Risk factors and risk groups	The risk groups are the ceftobiprole-treated patients to which copper reduction method for measuring urine glucose is applied.
Risk minimisation measures	Routine risk minimisation measures:

Important potential risk: INTERACTION WITH WITH COPPER REDUCTION TECHNIQUE TO MEASURE URINE GLUCOSE	
	• SmPC section 4.4 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None

Important potential risk: INTERACTION WITH JAFFÉ METHOD TO MEASURE CREATININE	
Evidence for linking the risk to the medicine	• Scientific literature: cephalosporins may interfere with Jaffé method to measure creatinine (Lettelier 1985). • Since the Jaffé is still widely employed as the method of choice for creatinine testing, this is considered as an important potential risk.
Risk factors and risk groups	The risk groups include the ceftobiprole-treated patients to which Jaffé method for measuring creatinine is applied.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None

Important potential risk: CYP DRUG INTERACTIONS	
Evidence for linking the risk to the medicine	• *In vitro* experiments: studies with ceftobiprole showed slight (8% to 28%) inhibitory potential towards CYP enzymes in the highest concentration range tested (50 to 100 µM). Because ceftobiprole is restricted to the extra-cellular water compartment, the potential of ceftobiprole to affect the CYP450-dependent metabolic clearance of co-administered drugs is considered very low. However, as the concentrations of ceftobiprole used in the *in vitro* studies were limited by solubility, the potential for CYP drug interactions cannot be excluded.
Risk factors and risk groups	Patients treated with drug metabolised via enzymes of the cytochrome P450 (CYP) family.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.5 • Legal status: administration by physician Additional risk minimisation measures: • None

Missing information:

Missing information: PREGNANCY AND LACTATION	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.6 and 5.3 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None

Missing information: PAEDIATRIC USE	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Paediatric investigation plan (PIP): – PIP study (BPR-PIP-001) – PIP study (BPR-PIP-002) – PIP study (BPR-PIP-003) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: SAFETY DATA IN PATIENTS WITH END-STAGE RENAL FAILURE	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post authorization safety study (PASS) (BPR-PAS-001) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: USE IN PATIENTS WITH HEPATIC IMPAIRMENT	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (BPR-PAS-001) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: USE IN HIV-POSITIVE PATIENTS, PATIENTS WITH NEUTROPENIA, IMMUNOCOMPROMISED PATIENTS, AND PATIENTS WITH MYELOSUPPRESION	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 • Legal status: administration by physician Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (BPR-PAS-001) See Section II.C of this summary for an overview of the post-authorisation development plan.

VI.II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Zevtera.

II.C.2 Other studies in post-authorisation development plan

Non-interventional post-authorisation safety study

- **BPR-PAS-001 - Retrospective chart review to evaluate the safety profile of ceftobiprole in patients with impaired hepatic or renal function or immunosuppression**

Purpose of the study:

Rationale

To estimate the incidence rate of treatment-emergent adverse events in patients treated with ceftobiprole, who have at least one of the following conditions:

- impaired renal function
- impaired hepatic function
- immunosuppression

Objectives

The objective of this study is to further characterise the safety profile of ceftobiprole, with particular emphasis on the following groups of patients:

- patients with severe renal impairment / end-stage renal disease
- patients with impaired baseline hepatic function
- patients with immunosuppression, including
  - HIV-positive patients
  - immunocompromised patients (any type or aetiology)
  - patients with baseline neutropenia
  - patients with baseline myelosuppression

Surveillance Programme

- **BSAC Respiratory Resistance Surveillance Programme**

Purpose of the study:

Rationale

To estimate the incidence of antimicrobial resistance in respiratory tract pathogens by a long-term surveillance approach and to identify any changes in pathogen susceptibility that may impact on subjects treated.

Objectives

Determination of the antimicrobial susceptibility of currently circulating lower respiratory tract isolates of community-acquired *Streptococcus pneumoniae, Haemophilus influenzae*

and *Moraxella catarrhalis*, and hospital-acquired *Staphylococcus aureus*, *Pseudomonas spp.*, *Acinetobacter spp.*, and *Enterobacteriaceae.*

- **BSAC Bacteraemia Resistance Surveillance Programme summary**

Purpose of the study:

Rationale

To estimate the incidence of antimicrobial resistance in pathogens causing bacteraemia by a long-term surveillance approach and to identify any changes in pathogen susceptibility that may impact on subjects treated.

Objectives

Determination of the antimicrobial susceptibility of currently circulating bacterial isolates from clinically significant bacteraemia.

- **IHMA-2197 - Surveillance of Ceftobiprole Activity against Clinical Isolates from European Medical Centers**

Purpose of the study:

Rationale

To investigate on a European level; whether there is a change in susceptibility of bacterial clinical isolates to ceftobiprole.

Objectives

Characterization of *in vitro* activity of ceftobiprole against a collection of currently circulating bacteria.

Paediatric Investigation Plan

- **BPR-PIP-001 - An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in neonate and infant subjects aged up to 3 months undergoing treatment with systemic antibiotics**

Purpose of the study:

Rationale

Since little information on pharmacokinetics and safety of ceftobiprole in neonates and infants was available in clinical trials conducted prior to auhtorsation of the antibiotic, this study is intended to provide further data in this respect.

Objectives

To characterise the pharmacokinetics, pharmacokinetics and tolerabily of single doses of ceftobiprole in neonates and infants aged ≤ 3 months.

- **BPR-PIP-002- A multicentre, randomized, investigator-blind, active-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in paediatric patients aged from 3 months to less than 18**

years with hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalisation

Purpose of the study:

Rationale

Little information on safety and efficacy of ceftobiprole in children and adolescents was available in clinical trials conducted prior to auhtorsation of the antibiotic. This study aims at providing further data in this respect.

Objectives

The primary objective is to characterise the safety profile of ceftobiprole in paediatric patients with HAP or CAP requiring hospitalisation and intravenous (IV) antibiotic therapy.

- **BPR-PIP-003- Multicentre, open label study to evaluate the safety, tolerability, pharmacokinetics and efficacy multiple doses of ceftobiprole in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis.**

Purpose of the study:

Rationale

Little information on the safety of ceftobiprole in neonates and infants was available in clinical trials conducted prior to auhtorsation of the antibiotic.

Objectives

The primary objective is to characterise the adverse event profile of ceftobiprole in term and pre-term neonates and infants ≤ 3 months with late-onset sepsis.

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