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Subject: VOLUNTARY RECALL OF BATCH SPECIFIC CEFTOLOZANE + TAZOBACTAM (ZERBAXA) 1G/500 MG POWDER FOR INJECTION (IV) / DR-XY45714
(RECALL LEVEL 3 – DISTRIBUTOR LEVEL)

This is to inform the public and concerned healthcare professionals that Merck Sharp & Dohme (I.A.) LLC, a Philippine subsidiary of Merck & Co., Inc., has notified the Food and Drug Administration (FDA), regarding the voluntary recall of the affected batches of Ceftolozane + Tazobactam (Zerbaxa®) 1g/500 mg Powder for Injection (IV). The details of the product are as follows:

PRODUCT AND REGISTRATION NO.:
Ceftolozane + Tazobactam (Zerbaxa®) 1g/500 mg Powder for Injection (IV) / DR-XY45714

AFFECTED BATCHES WITH MFG. AND EXP. DATE:

Batch No.	Manufacturing Date	Expiration Date
T005704	20 September 2019	28 February 2022
T008766	17 September 2019	28 February 2022
T017971	09 November 2019	30 April 2022
T022701	18 November 2019	30 April 2022
T025464	18 November 2019	30 April 2022

HISTORY OF TRIGGER/HAZARD OR REASON FOR RECALL AND ACTIONS:
The results of routine post-manufacture release sterility testing of six batches of Ceftolozane + Tazobactam (Zerbaxa®), manufactured in September and October 2020, did not meet specification. The batch numbers tested were SP1685, SP1688, SP1698, SP1700, SP1704, and SP1706. *Ralstonia pickettii* isolates were identified in four of the six batches. Additionally, the results of sterility testing on importation, by MSD Mirabel, of another batch of Ceftolozane + Tazobactam (Zerbaxa®), manufactured in July 2020, did not meet specification. *Ralstonia pickettii* isolates were identified in that case, too. That batch number was SP1678. These seven batches remain within MSD's control.

On 04 December 2020, molecular typing of the *Ralstonia pickettii* isolated during the sterility testing of two batches tested at Steri-Pharma and one batch tested at MSD Mirabel identified above confirmed that the isolates were from the same strain source. One of the batches in which *Ralstonia pickettii* isolates were identified was manufactured at Steri-Pharma in July 2020, prior to the site's most recent successful aseptic process simulation (APS), in August 2020. The other four batches in which *Ralstonia pickettii* isolates were identified were manufactured at Steri-Pharma after the August 2020 APS, potentially indicating that there was a common source of contamination present both before and after the successful August 2020 APS. Investigation of the Steri-Pharma and MSD Mirabel sterility testing laboratories has not indicated a laboratory-related root cause. Extensive investigations at Steri-Pharma, ACS, and Anxin are underway, with MSD and

other subject matter experts on-site. We are working to identify the root cause of the issue as quickly as possible.

A minimum inhibitory concentration (MIC) assay was performed on the *Ralstonia pickettii* isolated in the Ceftolozane + Tazobactam (Zerbaxa®) drug product identified above. This testing showed that all the isolates, including the control isolate, demonstrated large zones of inhibition. Based on these results, the isolates are considered susceptible to Ceftolozane + Tazobactam (Zerbaxa®). The original safety assessment was updated on 24 December 2020 to reflect the MIC assay results:

"While the investigation has yet to identify the root cause and cannot definitively determine the bioburden load in a given vial or batch of Ceftolozane + Tazobactam (Zerbaxa®), the available evidence supports the determination that the presence of viable *R. pickettii* in a final filled vial is a sporadic, random defect. Moreover, *R. pickettii* requires water and warm temperatures to proliferate, the identified isolates are sensitive to Ceftolozane + Tazobactam (Zerbaxa®), and there is a short period of time between reconstitution and use of the Ceftolozane + Tazobactam (Zerbaxa®) powder, the Ceftolozane + Tazobactam (Zerbaxa®) currently released to the commercial market and for clinical trial supply is at low risk to contain viable *R. pickettii* in sufficient quantities to cause serious adverse health consequences, such as life-threatening sepsis or death. This position is further substantiated by the lack of any safety signals detected through routine pharmacovigilance surveillance activities, as well as the comprehensive review of the post-marketing Adverse Event and Product Quality Complaint databases for this investigation. While this is reassuring, it does not alter the fact that a potential safety risk remains and is greatest for immunocompromised and critically-ill adults and neonates, but the probability is extremely remote for all populations."

Table 1, below, summarizes the probability of harm for the overall and high-risk populations.

Table 1. Probability of Harm – Overall and High-Risk Populations

Probability of Harm	Serious Adverse Health Consequences		Medically Reversible or Transient Adverse Health Consequences	
	Overall population	High-Risk	Overall population	High-Risk
Definite				
Likely				
Unlikely				
Remote				
Extremely Remote	**X**	**X**	**X**	**X**

INDICATIONS OF THE PRODUCT:

Ceftolozane + Tazobactam (Zerbaxa®) is indicated for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI).

INSTRUCTIONS TO THE GENERAL PUBLIC REGARDING THE RECALL OF THE PRODUCT:

Distributor and Healthcare Providers have been notified regarding this voluntary recall - up to the DISTRIBUTOR LEVEL.

COMPANY CONTACT DETAILS:

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FDA ADR REPORTING STATEMENT:

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph or through https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=PH".