ザバクサ配合点滴静注用
に関する資料

MSD 株式会社

CTD 第 1 部
1.5 起原又は発見の経緯及び開発の経緯

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略号及び用語の定義

略語（又は用語）	定義	
%$fT>C_T$	Time as percentage of the dosing interval that the free drug concentration remains above the threshold	遊離型薬物濃度が閾値濃度を超えている時間の投与間隔に対する割合
%$fT>$MIC	Time as percentage of the dosing interval that the free drug concentration exceeds the MIC	遊離型薬物濃度がMICを超えている時間の投与間隔に対する割合
Ceftolozane	Ceftolozane sulfate	セフトロザン硫酸塩
CL_{CR}	Creatinine clearance	クレアチニンクリアランス
C_T	Threshold concentration	閾値濃度
eCTD	Electronic Common Technical Document	電子化コモン・テクニカル・ドキュメント
ELF	Epithelial lining fluid	肺上皮被覆液
ITT	Intent-to-treat	―
MIC	Minimum inhibitory concentration	最小発育阻止濃度
MK-7625A	Tazobactam/ceftolozane	タゾバクタムナトリウム／セフトロザン硫酸塩
PK-PD	Pharmacokinetics-pharmacodynamics	薬物動態－薬力学
QTc	Corrected QT interval	補正したQT間隔
Tazobactam	Tazobactam sodium	タゾバクタムナトリウム
TOC	Test of cure	治癒判定
VABP	Ventilator-associated bacterial pneumonia	人工呼吸器関連肺炎
Ventilated HABP	Ventilated Hospital-acquired bacterial pneumonia	院内肺炎発症後に人工呼吸器を装着した院内肺炎
VNP	Ventilated nosocomial pneumonia	人工呼吸器を装着している院内肺炎

1.5　起原又は発見の経緯及び開発の経緯

1.5.1　起原又は発見の経緯

MK-7625A は、抗緑膿菌活性を有する新規のセファロスポリン系抗菌薬である Ceftolozane（セフトロザン硫酸塩：セフトロザン）に β-ラクタマーゼ阻害剤である Tazobactam（タゾバクタムナトリウム：タゾバクタム）を配合した注射用配合剤である。

本邦において MK-7625A は、2019年1月に膀胱炎、腎盂腎炎、腹膜炎、腹腔内膿瘍、胆嚢炎、肝膿瘍に対して1.5 g（タゾバクタム 0.5 g 及びセフトロザン 1 g）の1日3回静脈内投与が承認された。また、米国では2019年6月に、欧州連合では2019年8月に院内肺炎に対して3 g（タゾバクタム1 g 及びセフトロザン 2 g）の1日3回静脈内投与が承認された。

1.5.2　開発の経緯

本申請の臨床データパッケージには第Ⅰ相試験3試験及び第Ⅲ相試験1試験を含めた[表 1.5-1]。なお、028試験及び018試験の結果は、初回申請時に提出済みである（eCTD 受付番号300215001）。開発の経緯を[図 1.5-1]に示す。

表 1.5-1　製造販売承認事項一部変更承認申請の臨床データパッケージ

区分	日本人試験	非日本人試験
第Ⅰ相		非日本人細菌性肺炎患者を対象とした肺への移行性試験（007試験：参考資料）[2.7.6.2.1 項]
		非日本人健康被験者を対象とした反復投与試験（028試験†：参考資料）
	日本人、中国人、白人健康被験者を対象とした単回投与試験（018試験‡：参考資料）	
第Ⅲ相	人工呼吸器装着下の成人院内肺炎患者を対象とした国際共同試験（008試験：評価資料）[2.7.6.3.1 項]	

† 初回申請資料における試験名：CXA-MD-11-07試験（eCTD 受付番号300215001、資料5.3.3.1.4: 11-07）
‡ 初回申請資料における試験名：CXA-EB-13-05試験（eCTD 受付番号300215001、資料5.3.3.1.5: 13-05）

1.5.2.1　第Ⅰ相試験の概要

これまでに臨床薬理試験として第Ⅰ相試験10試験を実施し、MK-7625A の安全性、薬物動態、内因性及び外因性要因の影響、組織分布［肺上皮被覆液（ELF）中薬物動態］及び QTc 間隔に及ぼす影響を評価した。これらの臨床薬理試験の結果は、尿路及び腹腔内感染症の適応についての初回申請時に既に評価されている。本申請では MK-7625A 3 g 投与の根拠として、臨床薬理試験3試験のデータを用いるが、初回申請時に028試験及び018試験は提出済みのため、新たに実施した007試験のデータのみを提出する。

007試験は、人工呼吸器装着中の細菌性肺炎及び重症患者を対象とした MK-7625A（0.75、1.5又

は3 g）を静脈内投与した際の血漿中薬物動態及び肺への移行性を評価する第 I 相、プロスペクティブ、無作為化、非盲検、多施設共同試験であり、36例が組み入れられた。

人工呼吸器装着及び標準的な抗菌薬投与下の細菌性肺炎（確定又は疑い）患者を対象にクレアチニンクリアランス（CL_{CR}／Cockcroft-Gault 計算式で算出）に応じて MK-7625A（0.75、1.5又は3 g）を8時間ごとに60分かけて3～6回反復静脈内投与した際、また、CL_{CR}が180 mL/min 以上の重症細菌性肺炎患者（Acute Physiology and Chronic Health Evaluation II スコア：12以上35以下）を対象に MK-7625A 3 g を60分かけて単回静脈内投与した際、忍容性は概して良好であった。

人工呼吸器装着及び標準的な抗菌薬投与下の細菌性肺炎（確定又は疑い）患者に CL_{CR} に応じて MK-7625A 0.75、1.5又は3 g を反復静脈内投与した際、ELF 中セフトロザン及びタゾバクタム濃度は、それぞれ血漿中濃度の約50%及び約62%であり、セフトロザン及びタゾバクタムの肺への移行が確認され、健康被験者での移行性（セフトロザン：約61%、タゾバクタム：約63%）と概して類似していた。また、セフトロザン及びタゾバクタムの PK-PD パラメータは、それぞれ、セフトロザンの遊離型薬物濃度が最小発育阻止濃度（MIC）を超えている時間の投与間隔に対する割合（%*f*T>MIC）及びタゾバクタムの遊離型薬物濃度が閾値濃度（C_T）を超えている時間の投与間隔に対する割合（%*f*T>C_T）であり、セフトロザンの平均%*f*T>MIC は、MIC が4及び8 μg/mL のいずれにおいても血漿及び ELF 中でそれぞれ約90%超及び100%で、タゾバクタムの平均%*f*T>C_T（1 μg/mL）は、血漿及び ELF 中でそれぞれ約80%及び100%であった。

CL_{CR} が180 mL/min 以上で APACHE II スコアが12以上35以下の重症細菌性肺炎患者については、血漿中セフトロザンの平均%*f*T>MIC は70%超で、タゾバクタムの平均%*f*T>C_T（1 μg/mL）は約60%であった。

1.5.2.2　　第Ⅲ相試験の概要

008試験は、人工呼吸器を装着している院内肺炎（VNP）［人工呼吸器関連肺炎（VABP）又は院内肺炎発症後に人工呼吸器を装着した院内肺炎（ventilated HABP）］患者を対象とした MK-7625A の静脈内投与による安全性及び有効性についてメロペネムと比較する、多施設共同、無作為化、二重盲検、第Ⅲ相国際共同試験であり、726例（MK-7625A 群362例、メロペネム群364例）が無作為化された。被験者には MK-7625A 3 g 又はメロペネム1 g を1日3回、8～14日間静脈内投与した。本試験では VNP に対する MK-7625A の有効性及び安全性を評価し、さらに日本では008試験に組み入れられた被験者のうち敗血症患者に対する MK-7625A の有効性及び安全性も評価した。

VNP 患者については、Intent-to-treat（ITT）集団における治癒判定（TOC）時点の臨床効果の有効率（主要評価項目）は MK-7625A 群で54.4%（197/362例）、メロペネム群で53.3%（194/364例）であり、メロペネムに対して非劣性であることが示された。また、ITT 集団における Day 28の全死亡率（重要な副次評価項目）は MK-7625A 群で24.0%（87/362例）、メロペネム群で25.3%（92/364例）であり、MK-7625A はメロペネムに対して非劣性であることが示された。

MK-7625A の安全性プロファイルはメロペネムと類似しており、忍容性は良好で、概して安全であった。

敗血症患者については、008試験の VNP 患者のうち100例（MK-7625A 群61例、メロペネム群39

例）が敗血症評価対象集団に含まれた。TOC 時点の臨床効果の有効率（主要評価項目）は MK-7625A 群で24.6%（15/61例）、メロペネム群で17.9%（7/39例）、TOC 時点の細菌学的効果の有効率（副次評価項目）は MK-7625A 群で49.2%（30/61例）、メロペネム群で41.0%（16/39例）であり、敗血症に対する MK-7625A の有効性はメロペネムと同程度であることが示された。敗血症患者における MK-7625A の忍容性は良好で、安全性プロファイルはメロペネムと類似しており、概して安全であった。

本試験では13例（MK-7625A 群5例、メロペネム群8例）が日本人被験者であった。全般的に MK-7625A は日本人集団においても VNP に対して有効性を示し、概して安全であった。なお、敗血症評価対象集団に含まれた日本人はメロペネム群の1例のみであった。

以上より、MK-7625A 3 g の1日3回静脈内投与は VNP 患者及び敗血症患者に対して有効性を示し、概して安全であったことから、本邦での肺炎及び敗血症の適応追加について製造販売承認事項一部変更承認申請を行うこととした。

図 1.5-1　開発の経緯

試験項目		試験名
薬理試験		薬効薬理
臨床試験	第Ⅰ相（参考資料）	007試験：非日本人細菌性肺炎患者を対象とした肺への移行性試験
		028試験：非日本人健康被験者を対象とした反復投与試験
		018試験：日本人、中国人、白人健康被験者を対象とした単回投与試験
	第Ⅲ相（評価資料）	008試験：VNP 患者を対象とした国際共同試験

図中の数字は月を示す。======：国内及び海外で実施、--------：海外で実施

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1.6 外国における使用状況等に関する資料

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1.6　外国における使用状況等に関する資料

1.6.1　外国における使用状況等

2019年9月10日現在、MK-7625A は1.5 g の用量において、下記の効能・効果で、米国、欧州連合（EU）を含む72の国又は地域で承認されている。米国及び EU での MK-7625A の承認状況を[表1.6.1-1]に示す。また、米国及び EU では、3 g の用量で院内肺炎の適応追加申請をそれぞれ2018年12月4日及び2018年11月21日に実施し、米国では2019年6月3日、EU では2019年8月23日に承認を取得した。

表 1.6.1-1　　海外での主な承認状況

国名	販売名	承認年月日	剤型・含量	効能・効果	用法・用量
米国	ZERBAXA	複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症：2014年12月19日 院内肺炎及び人工呼吸器関連肺炎：2019年6月3日	1バイアル中ceftolozane 1 g（ceftolozane sulfate として1.147 g）及びtazobactam 0.5 g（tazobactam sodium として0.537 g）を含有する注射剤	・複雑性腹腔内感染症 ・腎盂腎炎を含む複雑性尿路感染症 ・院内肺炎及び人工呼吸器関連肺炎	複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症：ZERBAXA 1.5 g（ceftolozane 1 g/tazobactam 0.5 g）を1時間かけて8時間ごとに静脈内投与する。 院内肺炎及び人工呼吸器関連肺炎：ZERBAXA 3 g（ceftolozane 2 g/tazobactam 1 g）を1時間かけて8時間ごとに静脈内投与する。 ＜投与期間＞ 複雑性腹腔内感染症†：4～14日間 腎盂腎炎を含む複雑性尿路感染症：7日間 院内肺炎及び人工呼吸器関連肺炎：8～14日間 †メトロニダゾール500 mg（8時間ごとに静脈内投与）と併用
EU	ZERBAXA	複雑性腹腔内感染症、急性腎盂腎炎及び複雑性尿路感染症2015年9月18日 人工呼吸器関連肺炎を含む院内肺炎：2019年8月23日	1バイアル中、ceftolozane sulfate（ceftolozane として1 g）及びtazobactam sodium（tazobactam として0.5 g）を含有する注射剤	・複雑性腹腔内感染症 ・急性腎盂腎炎 ・複雑性尿路感染症・人工呼吸器関連肺炎を含む院内肺炎	ZERBAXA 1.5 g（ceftolozane 1 g/tazobactam 0.5 g）を1時間かけて8時間ごとに静脈内投与する。 ＜投与期間＞ 複雑性腹腔内感染症‡：4～14日間 複雑性尿路感染症及び急性腎盂腎炎：7日間 人工呼吸器関連肺炎を含む院内肺炎：8～14日間 ‡嫌気性病原菌が疑われる場合はメトロニダゾールを併用すること

1.6.2　　外国の添付文書

2019年9月10日現在、MK-7625A は、米国及び EU で、院内肺炎及び人工呼吸器関連肺炎の適応追加で承認を取得している。

MK-7625A 1.5 g の用量で複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症を適応とし、MK-7625A 3 g の用量で院内肺炎及び人工呼吸器関連肺炎を適応とする米国の添付文書の要約を[1.6.2.1項]に示し、原文を[1.6.2.2項]に添付する。

また、MK-7625A 1.5 g の用量で複雑性腹腔内感染症、急性腎盂腎炎及び複雑性尿路感染症を適応とし、MK-7625A 3 g の用量で人工呼吸器関連肺炎を含む院内肺炎を適応とする EU の添付文書の要約を[1.6.2.1項]に示し、原文を[1.6.2.2項]に添付する。

1.6.2.1　　外国の添付文書の概要（和訳）

米国及び EU の添付文書の概要を要約する。販売名／販売会社名、剤型・含量、効能・効果、用法・用量、禁忌、警告、使用上の注意、薬物相互作用、副作用、特殊集団への投与、過量投与等について記載する。

1.6.2.1.1　　米国添付文書の概要（和訳）

販売名／販売会社名

販　売　名：ZERBAXA

販売会社名：Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., N.J., USA.

剤型・含量

ZERBAXA 1.5 g（ceftolozane/tazobactam）は、白色～黄色の無菌粉末で、単回投与調製用バイアルの注射剤である。1バイアル中、ceftolozane1 g（ceftolozane sulfate として1.147 g）及び tazobactam 0.5 g（tazobactam sodium として0.537 g）を含有する。

効能・効果

複雑性腹腔内感染症

ZERBAXA はメトロニダゾールとの併用で、18歳異常の患者における以下のグラム陰性菌及びグラム陽性菌による複雑性腹腔内感染症（cIAI）に対する適応を取得している。

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Bacteroides fragilis
Streptococcus anginosus
Streptococcus constellatus
Streptococcus salivarius

腎盂腎炎を含む複雑性尿路感染症

ZERBAXA は、18歳以上の患者における、本剤に感受性の以下のグラム陰性菌による腎盂腎炎を含む複雑性尿路感染症（cUTI）に対する適応を取得している。

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

院内肺炎及び人工呼吸器関連肺炎

ZERBAXA は、18歳以上の患者における、本剤に感受性の以下のグラム陰性菌による院内肺炎及び人工呼吸器関連肺炎（HABP/VABP）に対する適応を取得している。

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

効能・効果に関連する使用上の注意

薬剤耐性菌の発現を防止し、ZERBAXA 及び他の抗菌薬の効果を維持するため、ZERBAXA は本剤に感受性の起炎菌によるものと確認されているか、強く疑われる感染症の治療又は予防に対してのみ使用すること。培養検査及び感受性検査のデータが得られている場合には、抗菌薬の選択又は変更の際にそれらを参考にする。そのようなデータがない場合、当該地域における疫学的傾向及び感受性パターンに基づいて経験的に治療法を選択する。

用法・用量

推奨用量

クレアチニン・クリアランス（CL_{CR}）が50 mL/min 超の18歳以上の患者の場合、cIAI 及び cUTI では ZERBAXA 注射剤1.5 g（ceftolozane 1 g/tazobactam 0.5 g）、HABP/VABP では3 g（ceftolozane 2 g/tazobactam 1 g）を1時間かけて8時間ごとに静脈内投与する。投与期間は感染症の程度、感染部位、患者の臨床経過及び細菌学的経過に基づき判断する[表 1.6.2-1]。

表 1.6.2-1　　クレアチニン・クリアランス>50 mL/min の患者における適応症ごとの ZERBAXA の投与方法

適応症	投与量	投与間隔	投与時間	投与期間
複雑性腹腔内感染症†	1.5 g	8時間ごと	1時間	4～14日間
腎盂腎炎を含む複雑性尿路感染症	1.5 g	8時間ごと	1時間	7日間
院内肺炎及び人工呼吸器関連肺炎（HABP/VABP）	3 g	8時間ごと	1時間	8～14日間
†メトロニダゾール500 mg（8時間ごとに静脈内投与）と併用				

腎機能障害患者での用量調節

クレアチニン・クリアランス（CL_{CR}）が50 mL/min 以下の患者については用量調節が必要である[表 1.6.2-2]。いずれの用量も1時間かけて投与する。腎機能の変動がみられる患者の場合、CL_{CR}を少なくとも1日1回測定し、その測定値に従い用量調節すること（「特殊集団への投与」及び「臨床薬理」の項（添付文書原文）参照）。

表 1.6.2-2　　クレアチニン・クリアランス≤50 mL/min の成人患者における ZERBAXA の投与方法

推定 CL_{CR}（mL/min）†	複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症	院内肺炎及び人工呼吸器関連肺炎（HABP/VABP）
30～50	750 mg（ceftolozane 500 mg/tazobactam 250 mg）を8時間ごとに静脈内投与	1.5 g（ceftolozane 1 g/tazobactam 0.5 g）を8時間ごとに静脈内投与
15～29	375 mg（ceftolozane 250 mg/tazobactam 125 mg）を8時間ごとに静脈内投与	750 mg（ceftolozane 500 mg/tazobactam 250 mg）を8時間ごとに静脈内投与
血液透析中の末期腎不全	負荷用量として750 mg（ceftolozane 500 mg/tazobactam 250 mg）を単回投与し、その後は維持用量として150 mg（ceftolozane 100 mg/tazobactam 50 mg）を8時間ごとに投与（透析を受ける日は透析終了後速やかに投与を開始）	負荷用量として2.25 g（ceftolozane 1.5 g/tazobactam 0.75 g）を単回投与し、その後は維持用量として450 mg（ceftolozane 300 mg/tazobactam 150 mg）を8時間ごとに投与（透析を受ける日は透析終了後速やかに投与を開始）
CL_{CR}：クレアチニン・クリアランス †Cockcroft-Gault 式により推定した CL_{CR}		

注射液の調製

ZERBAXA に静菌作用を有する保存剤は含まれていない。本剤の注射液は無菌的に調製する。

調製方法

ZERBAXA の各バイアルに注射用水又は米国薬局方0.9%注射用生理食塩液10 mL を加えて緩やかに振盪し、溶解液を調製する。溶解後の液量は1バイアル当たり約11.4 mL となる。注意：溶解液を直接投与しないこと。

各用量の注射液を調製する際は、[表 1.6.2-3]に従い必要量をバイアルから抜き取り、米国薬局方0.9%注射用生理食塩液又は米国薬局方5%ブドウ糖注射液100 mL の入った輸液バッグに加える。1.5 g 以上の用量では、1本目のバイアルと同様に2本目のバイアルで溶解液を調製し、[表 1.6.2-3]に示す必要量をバイアルから抜き取り、同じ輸液バッグに加える。

表 1.6.2-3　　調製方法

ZERBAXA	バイアルからの抜き取り量
3 g（ceftolozane 2 g/tazobactam 1 g）	2本のバイアルから各11.4 mL（2本のバイアルの全量）
2.25 g（ceftolozane 1.5 g/tazobactam 0.75 g）	1本目のバイアルから11.4 mL（全量）及び2本目のバイアルから5.7 mL
1.5 g (ceftolozane 1 g/tazobactam 0.5 g)	11.4 mL（全量）
750 mg (ceftolozane 500 mg/tazobactam 250 mg)	5.7 mL
450 mg (ceftolozane 300 mg/tazobactam 150 mg)	3.5 mL
375 mg (ceftolozane 250 mg/tazobactam 125 mg)	2.9 mL
150 mg (ceftolozane 100 mg/tazobactam 50 mg)	1.2 mL

本剤の使用前に微粒子や変色がないか目視で確認する。ZERBAXA 注射液は無色～微黄色の澄明な液体である。色がこの範囲内であれば力価に影響はない。

配合変化

ZERBAXA と他の薬剤との配合変化は不明である。ZERBAXA を他の薬剤と混和、又は他の薬剤を含む溶液に添加しないこと。

調製後溶液の保存

注射用水又は0.9%注射用生理食塩液で調製した ZERBAXA 溶解液は、1時間以内に輸液バッグへ移して希釈すること。

0.9%注射用生理食塩液又は5%ブドウ糖注射液で希釈後の ZERBAXA 注射液は、室温保存で24時間、2～8°C（36～46°F）の冷蔵保存で7日間安定である。

溶解後の ZERBAXA 溶液又は希釈後の ZERBAXA 注射液を凍結させないこと。

禁忌

ZERBAXA の成分（ceftolozane/tazobactam）、piperacillin/tazobactam 又は他の β-ラクタム系抗菌薬に対する重度の過敏症の既往歴のある患者での使用は禁忌である。

警告及び使用上の注意

ベースライン時における CL_{CR} が30～50 mL/min の患者での有効性の低下：

cIAI 患者を対象とした第Ⅲ相試験の部分集団解析では、ベースライン時に CL_{CR} が50 mL/min 超の患者と比較して、CL_{CR} が30～50 mL/min であった患者の臨床的治癒率は低かった[表 1.6.2-4]。

この集団での臨床的治癒率の低下は、ZERBAXA+メトロニダゾール群の方がメロペネム群よりも顕著であった。同様の傾向は cUTI 患者を対象とした試験でも認められた。腎機能の変動がみられる患者の場合、CL_{CR} を少なくとも1日1回測定し、その測定値に従い用量調節すること（「用法・用量」の項（添付文書原文）参照）。

表 1.6.2-4　　ベースライン時の腎機能別の cIAI の第Ⅲ相試験の臨床的治癒率（MITT 集団）

ベースライン時の腎機能	ZERBAXA+メトロニダゾール n/N (%)	メロペネム n/N (%)
CL_{CR}>50 mL/min	312/366 (85.2)	355/404 (87.9)
CL_{CR} 30～50 mL/min	11/23 (47.8)	9/13 (69.2)

過敏症反応

β-ラクタム系抗菌薬の投与により重篤な過敏症（アナフィラキシー）反応が認められており、死亡例も報告されている。

ZERBAXA の投与を開始する前に、他のセファロスポリン系抗菌薬、ペニシリン系抗菌薬又は他の β-ラクタム系抗菌薬に対する過敏症反応の既往歴について十分な問診を行うこと。セファロスポリン系、ペニシリン系又は他の β-ラクタム系抗菌薬には交差反応性が認められるため、これらの抗菌薬に対するアレルギーの既往歴がある患者には本剤を慎重に投与すること。ZERBAXA に対するアナフィラキシー反応が現れた場合には投与を中止し、適切な処置を行うこと。

C. difficile 関連下痢症

ZERBAXA を含むほぼすべての抗菌薬で、抗菌薬の全身投与による *C. difficile* 関連下痢症が報告されており、その程度も軽度の下痢から致命的な大腸炎まで様々である。抗菌薬の投与により腸内細菌叢が損なわれ、それにより *C. difficile* の異常増殖が生じやすくなる。

C. difficile は、*C. difficile* 関連下痢症の発症の一因となるトキシン A 及び B を産生する。抗菌薬の投与後の患者に下痢がみられた場合、*C. difficile* 関連下痢症の可能性を検討すること。抗菌薬の投与から2ヵ月以上経ってから *C. difficile* 関連下痢症が報告されていることから、既往歴について慎重に問診を行うこと。

C. difficile 関連下痢症が確認された場合、可能であれば、*C. difficile* に対する抗菌薬以外の投与を中止すること。必要な場合は、体液及び電解質管理を行い、蛋白質摂取を補給し、*C. difficile* の抗菌薬治療をモニタリングし、臨床的に必要であれば外科的評価を実施すること。

薬剤耐性菌の発現

ZERBAXA に感受性の起炎菌によるものと確認されているか、強く疑われる感染症以外又は予防的に本剤を投与しても、患者にベネフィットが得られる可能性は低く、耐性菌の発現リスクが高くなる。

副作用

以下の重篤な副作用は、「警告及び使用上の注意」の項で詳細に考察する：

過敏症反応（「警告及び使用上の注意」の項（添付文書原文）参照）。

C. difficile 関連下痢症（「警告及び使用上の注意」の項（添付文書原文）参照）。

臨床試験での使用経験

臨床試験は、多種多様な条件下で実施されるため、ある薬剤の臨床試験での副作用発現頻度と他の薬剤の臨床試験における副作用発現頻度とを直接比較できない。また、臨床試験での副作用発現頻度は、実際の診療において認められる副作用発現頻度を反映しない可能性がある。

複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症 cIAI 患者及び cUTI 患者を対象とした第Ⅲ相実薬対照試験において、ZERBAXA（1.5 g を8時間ごとに投与、腎機能障害の程度に基づき適宜調節）を1,015例、対照薬を1,032例に最長14日間投与した。対照薬は、cUTI 患者ではレボフロキサシン750 mg を1日1回、cIAI 患者ではメロペネム1 g を8時間ごととした。各投与群及び各適応症を通じ、治験薬の投与を受けた被験者の平均年齢は48～50歳（範囲：18～92歳）であった。いずれの適応症でも、被験者の約25%が65歳以上であった。cUTI 試験の被験者の大部分（75%）は女性であり、cIAI 試験の被験者の58%は男性であった。いずれの適応症でも、被験者の大部分（70%超）は東ヨーロッパで組み入れられ、白人であった。

第Ⅲ相試験で ZERBAXA を投与した被験者に高頻度で認められた副作用（いずれかの適応で5%以上）は、悪心、下痢、頭痛及び発熱であった。cIAI 患者及び cUTI 患者を対象とした第Ⅲ相試験で ZERBAXA を投与した被験者で1%以上に認められた副作用を[表 1.6.2-5]に示す。

表 1.6.2-5　　cIAI 患者及び cUTI 患者を対象とした第Ⅲ相試験で認められた副作用（ZERBAXA を投与した被験者で 1%以上）

基本語	複雑性腹腔内感染症		腎盂腎炎を含む複雑性尿路感染症	
	ZERBAXA† (N=482) n (%)	メロペネム (N=497) n (%)	ZERBAXA† (N=533) n (%)	レボフロキサシン (N=535) n (%)
悪心	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
頭痛	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
下痢	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
発熱	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
便秘	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
不眠症	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)
嘔吐	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
低カリウム血症	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
ALT 増加	7 (1.5)	5 (1)	9 (1.7)	5 (0.9)
AST 増加	5 (1)	3 (0.6)	9 (1.7)	5 (0.9)
貧血	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
血小板増加	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
腹痛	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
不安	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
浮動性めまい	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
低血圧	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)
心房細動	6 (1.2)	3 (0.6)	1 (0.2)	0
発疹	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)

†ZERBAXAは1 5 gの用量で8時間ごとに静脈内投与し、腎機能に応じて用量調節した。cIAI患者を対象とした試験ではZERBAXAとメトロニダゾールを併用投与した。

投与中止に至った有害事象は ZERBAXA 群2.0%（20/1,015例）、対照群1.9%（20/1,032例）に認められた。投与中止に至った腎機能障害（腎機能障害、腎不全及び急性腎不全を含む）は、ZERBAXA 群0.5%（5/1,015例）に認められ、対照群では認められなかった。

死亡率の増加

cIAI 患者を対象とした試験（第Ⅱ及びⅢ相）で、死亡は ZERBAXA 群の2.5%（14/564例）、メロペネム群の1.5%（8/536例）に認められた。死因は様々であり、感染症の悪化又は合併症、手術及び基礎疾患が含まれた。

cIAI 患者及び cUTI 患者を対象とした第Ⅲ相試験で認められた発現頻度が低い副作用

ZERBAXA を投与した被験者に1%未満の頻度で認められた副作用を以下に示す。

心臓障害	頻脈、狭心症
胃腸障害	胃炎、腹部膨満、消化不良、鼓腸、麻痺性イレウス
一般・全身障害および投与部位の状態	注入部位反応
感染症および寄生虫症	カンジダ症（中咽頭カンジダ症及び外陰部腟カンジダ症）、真菌性尿路感染

臨床検査	血清γ-グルタミルトランスペプチダーゼ増加、血清アルカリホスファターゼ増加、クームス試験陽性
代謝および栄養障害	高血糖、低マグネシウム血症、低リン酸血症
神経系障害	虚血性脳卒中
腎および尿路障害	腎機能障害、腎不全
呼吸器、胸郭および縦隔障害	呼吸困難
皮膚および皮下組織障害	蕁麻疹
血管障害	静脈血栓症

院内肺炎及び人工呼吸器関連肺炎（HABP/VABP）

HABP/VABP 患者を対象とした第Ⅲ相実薬対照試験において、ZERBAXA（3 g を8時間ごとに投与、腎機能障害の程度に基づき適宜調節）を361例、対照薬（メロペネム1 g を8時間ごとに投与）を359例に最長14日間投与した。治験薬の投与を受けた被験者の平均年齢は、両投与群で60歳（範囲：18～98歳）であった。被験者の約44%が65歳以上であった。被験者の大部分（71%）は男性であった。無作為割付け時に、すべての被験者は人工呼吸器を装着しており、92%は集中治療室で治療を受けている患者であった。APACHE Ⅱ スコアの中央値は17、被験者の33%でベースライン時の APACHE Ⅱ スコアが20以上であり、本試験に組み入れられた被験者の大部分が重症患者であることが示された。

HABP/VABP 患者を対象とした第Ⅲ相試験で ZERBAXA を投与した被験者で2%以上に認められた副作用を[表 1.6.2-6]に示す。

表 1.6.2-6　　HABP/VABP 患者を対象とした第Ⅲ相試験で認められた副作用（ZERBAXA を投与した被験者で2%以上）

基本語	ZERBAXA† (N=361) n (%)	メロペネム (N=359) n (%)
肝トランスアミナーゼ増加‡	43 (11.9)	26 (7.2)
腎機能障害／腎不全§	32 (8.9)	22 (6.1)
下痢	23 (6.4)	25 (7.0)
頭蓋内出血‖	16 (4.4)	5 (1.4)
嘔吐	12 (3.3)	10 (2.8)
クロストリジウム・ディフィシレ大腸炎¶	10 (2.8)	2 (0.6)

†ZERBAXA は3 g の用量で8時間ごとに静脈内投与し、腎機能に応じて用量調節した。
‡アラニンアミノトランスフェラーゼ増加、アスパラギン酸アミノトランスフェラーゼ増加、肝酵素上昇、高トランスアミナーゼ血症及び肝機能検査異常を含む。
§急性腎不全、無尿、高窒素血症、乏尿、腎前性腎不全、腎不全及び腎機能障害を含む。
‖小脳出血、脳血腫、脳出血、頭蓋内出血、出血性卒中、卒中の出血性変化、脳室内出血、くも膜下出血及び硬膜下血腫を含む。
¶クロストリジウム・ディフィシレ大腸炎、クロストリジウム・ディフィシレ感染及びクロストリジウム検査陽性を含む。

投与中止に至った副作用はZERBAXA群1.1%（4/361例）、メロペネム群1.4%（5/359例）に認められた。

HABP/VABP患者を対象とした第Ⅲ相試験で認められた発現頻度が低い副作用
ZERBAXAを投与した被験者に2%未満の頻度で認められた副作用を以下に示す。

臨床検査	血中アルカリホスファターゼ増加、γ-グルタミルトランスフェラーゼ増加、直接クームス試験陽性

臨床検査値

ZERBAXAの投与中は、直接クームス試験で陽性となることがある。cIAI患者及びcUTI患者を対象とした臨床試験では、直接クームス試験でのセロコンバージョンの発現頻度は、ZERBAXA群0.2%、対照群0%であった。HABP/VABP患者を対象とした臨床試験では、直接クームス試験でのセロコンバージョンの発現頻度は、ZERBAXA群31.2%、メロペネム群3.6%であった。臨床試験では、いずれの投与群においても直接クームス試験が陽性となった患者で溶血が発現したことを裏付けるものはみられなかった。

薬物相互作用

健康被験者16例を対象とした臨床試験で、ceftolozane及びtazobactamに薬物相互作用は認められなかった。*In vitro*及び*in vivo*試験の結果から、治療域の血漿中薬物濃度のZERBAXAはCYPの基質及びトランスポーターと臨床的に意味のある薬物相互作用を示す可能性はないと考えられる。

薬物代謝酵素

*In vivo*では、ZERBAXAはCYPの基質ではないと考えられる。したがって、ZERBAXAはCYPの阻害薬又は誘導薬と臨床的に意義のある薬物相互作用を示す可能性はないと考えられる。

*In vitro*では、ceftolozane、tazobactam及びtazobactamのM1代謝物は、治療域の血漿中薬物濃度で、CYP1A2、CYP2B6、CYP2C8、CYP2C9、CYP2C19、CYP2D6又はCYP3A4に対する阻害作用は示さず、CYP1A2、CYP2B6又はCYP3A4に対する誘導作用も認められなかった。ヒト初代肝細胞の*in vitro*の誘導試験で、ceftolozane、tazobactam及びtazobactamの代謝物であるM1は、ヒト初代肝細胞でCYP1A2及びCYP2B6の酵素活性及びmRNAレベルを低下させ、治療域を超える血漿中薬物濃度でCYP3A4のmRNAレベルを低下させた。また、治療域を超える血漿中薬物濃度で、tazobactamの代謝物であるM1はCYP3A4の活性を低下させた。ヒトでの薬物相互作用試験でも、ZERBAXAはCYP1A2又はCYP3A4を介した阻害作用を示さないと考えられた。

膜トランスポーター

In vitro では、治療域の血漿中薬物濃度において、ceftolozane 及び tazobactam は P-糖蛋白質（P-gp）又は乳癌耐性蛋白質（BCRP）の基質ではなく、tazobactam は有機カチオントランスポーター（OCT）2の基質ではなかった。

Tazobactam は、*in vitro* で有機アニオントランスポーター（OAT）1及び OAT3の基質である。Tazobactam と OAT1及び OAT3阻害薬であるプロベネシドの併用により、tazobactam の $t_{1/2}$は71%延長した。OAT1又は OAT3の阻害薬を併用すると、tazobactam の血漿中濃度が上昇する可能性がある。

In vitro では、ceftolozane は、治療域の血漿中薬物濃度において、P-gp、BCRP、有機アニオン輸送ポリペプチド（OATP）1B1、OATP1B3、OCT1、OCT2、多剤耐性関連蛋白（MRP）、胆汁酸トランスポーター（BSEP）、OAT1、OAT3、multidrug and toxin extrusion（MATE）1又は MATE2-K の阻害作用を示さなかった。

In vitro では、tazobactam 及び tazobactam の M1代謝物は、治療域の血漿中薬物濃度において、P-gp、BCRP、OATP1B1、OATP1B3、OCT1、OCT2又は BSEP の阻害作用を示さなかった。Tazobactam は、*in vitro* でヒト OAT1及び OAT3を阻害し、50%阻害濃度（IC_{50}）値は、それぞれ118 μg/mL 及び147 μg/mL であった。ヒトでの薬物相互作用試験でも、ZERBAXA は OAT1又は OAT3を介した臨床的に意義のある阻害作用を示さないと考えられた。

<u>特殊集団への投与</u>

妊婦への投与

リスクの要約

重大な先天性欠損、自然流産、妊婦又は胎児への影響の薬物関連のリスクを評価するために、妊娠中の婦人に ZERBAXA、ceftolozane 又は tazobactam を投与したデータは得られていない。公開されている数十年間のプロスペクティブコホート研究、症例集積研究及び症例報告から得られたデータでは、妊娠中のセファロスポリンの使用と重大な先天性欠損、自然流産、妊婦又は胎児への影響との関連は認められなかった（「データ」参照）。マウス及びラットに血漿中 AUC 換算で 2 g 8時間ごと投与の最大臨床推奨用量のそれぞれ約3.5倍及び2倍の用量の ceftolozane、ラットに体表面積換算で1 g 8時間ごと投与の最大臨床推奨用量の約10倍の tazobactam を投与した際、器官形成期のげっ歯類において ceftolozane 又は tazobactam のいずれも胚・胎児毒性は認められなかった。妊娠及び授乳期の母動物に ceftolozane を静脈内投与及び tazobactam を腹腔内投与したラットの出生前及び出生後の発生に関する試験では、血漿中 AUC 換算で臨床推奨用量より低い用量の ceftolozane の投与で F1出生児に聴覚性驚愕反応の低下が認められ、臨床推奨用量の約4倍に相当する tazobactam の投与で母動物に体重増加量の減少及び死産児数の増加が認められ、体表面積換算で臨床推奨用量に相当する用量の投与で F1出生児の体重の減少の関連が認められた（「データ」参照）。

妊婦における重大な先天性欠損及び自然流産の背景リスクの推定は不明である。すべての妊娠には、先天性欠損、自然流産やその他の有害な転帰の背景リスクがある。米国の一般集団における臨床妊婦又は臨床的妊娠における重大な先天性欠損及び自然流産の背景リスクの推定値は、そ

れぞれ2～4%及び15～20%である。

データ

ヒトでのデータ

複数のセファロスポリンの試験からは、リスクの有無を明確に確定することはできないが、公開されている数十年間のプロスペクティブコホート研究、症例集積研究及び症例報告から得られたデータでは、妊娠中のセファロスポリンの使用と重大な先天性欠損、自然流産、妊婦又は胎児への影響との関連は認められなかった。複数のセファロスポリンの試験には、サンプル数が小さい、レトロスペクティブなデータ収集及び対照群が一貫していないなど、試験方法の限界がある。

動物でのデータ

CeftolozaneCeftolozane を投与したマウス及びラットの胚・胎児発生に関する試験では、器官形成期（妊娠6～15日）の母動物に ceftolozane を300、1,000及び2,000 mg/kg/日（マウス）、並びに器官形成期（妊娠6～17日）の母動物に ceftolozane を100、300及び1,000 mg/kg/日（ラット）まで静脈内投与した。マウスでは、最高用量の2,000 mg/kg/日（血漿 AUC 換算で2 g 8時間ごと投与の臨床推奨用量の約3.5倍）の投与で母動物、胚・胎児に毒性は認められなかった。ラットでは、胚・胎児毒性は認められなかったが、1,000 mg/kg/日の投与で母動物の体重増加量の減少が認められた。ラットでは、300 mg/kg/日の投与で母動物に毒性は認められず、1,000 mg/kg/日の投与で胚・胎児毒性は認められなかった（血漿 AUC 換算で臨床推奨用量のそれぞれ約0.7倍及び2倍）。

Ceftolozane を投与したラットの出生前及び出生後の発生に関する試験では、妊娠及び授乳期（妊娠6日～授乳20日）の母動物に ceftolozane を静脈内投与した結果、300 mg/kg/日以上の投与で生後60日の雄出生児に聴覚性驚愕反応の低下が認められた。ラットでは、血漿 AUC 換算で2 g 8時間ごと投与の臨床推奨用量より低い用量である100 mg/kg/日の投与で影響は認められなかった。

TazobactamTazobactam を投与したラットの胚・胎児発生に関する試験では、器官形成期（妊娠7～17日）の母動物に tazobactam 125、500及び3,000 mg/kg/日を静脈内投与した結果、3,000 mg/kg/日の高用量の投与で母動物に毒性（摂餌量及び体重増加量の減少）が認められたが、胚・胎児毒性は認められなかった。500 mg/kg/日の投与で母動物に毒性は認められず、3,000 mg/kg/日の投与で胚・胎児への影響は認められなかった（体表面積換算で1 g 8時間ごと投与の臨床推奨用量のそれぞれ約2倍及び10倍）。ラットでは tazobactam が胎盤を通過することが示された。Tazobactam の胎児中濃度は母動物の血漿中濃度の10%以下であった。

Tazobactam を投与したラットの出生前及び出生後の発生に関する試験では、妊娠後期から授乳期（妊娠17日～授乳21日）の母動物に tazobactam 40、320及び1,280 mg/kg/日を腹腔内投与した結果、1,280 mg/kg/日の高用量の投与で母動物に妊娠後期の摂餌量及び体重増加量の減少並びに死産児数の有意な増加との関連が認められた。F1出生児の身体発育、神経機能発達、受胎能力又は生殖能に影響は認められなかったが、320又は1,280 mg/kg/日を投与した母動物から生まれた F1出生児の体重は、生後21日に有意に低値を示した。F2世代の胎児には、検討したすべての用量で異常

は認められなかった。最大320 mg/kg/日を投与した母動物の生殖能への影響は認められず、40 mg/kg/日の投与でF1出生児の低体重は認められなかった（体表面積換算で1 g 8時間ごと投与の臨床推奨用量のそれぞれ約1.0倍及び0.1倍）。

授乳婦への投与

リスクの要約

Ceftolozane 又は tazobactam の母乳への移行に関するデータは得られていない。また、Ceftolozane 又は tazobactam の乳児への影響又は乳汁産生への影響に関するデータは得られていない。

授乳婦の ZERBAXA の臨床的必要性、授乳中の乳児への ZERBAXA の潜在的な副作用及び授乳婦の基礎疾患に加え、授乳の発育上及び健康上の利益を考慮して、授乳を中止するか、ZERBAXA の投与を中止するか決定しなければならない。

小児への投与

小児患者に対しての安全性及び有効性は確立していない。

高齢者への投与

cIAI 患者及び cUTI 患者を対象とした第Ⅲ相試験において ZERBAXA を投与された1,015例のうち、250例（24.6%）が65歳以上であり、113例（11.1%）が75歳以上であった。いずれの適応症でも、臨床試験での有害事象発現頻度は、いずれの投与群でも高齢者（65歳以上）で高かった。cIAI 患者を対象とした試験では、高齢者（65歳以上）での臨床的治癒率は、ZERBAXA+メトロニダゾール群69%（69/100例）、対照群82.4%（70/85例）であった。高齢者の部分集団でのこの所見は、cUTI 患者を対象とした試験では認められなかった。

HABP/VABP 患者を対象とした第Ⅲ相試験において ZERBAXA を投与された361例のうち、160例（44.3%）が65歳以上であり、83例（23.0%）が75歳以上であった。臨床試験での有害事象発現頻度は、いずれの投与群でも高齢者（65歳以上）で高かった。本試験では、高齢者（65歳以上）での Day 28の全死亡率は、ZERBAXA 群31.3%（50/160例）、対照群33.8%（54/160例）であり、投与群間で同程度であった。

ZERBAXA は主に腎排泄されることから、腎機能障害患者では副作用の発現リスクが上昇する可能性がある。高齢者では腎機能が低下していることが多いため、用量選択には注意を払うこと。また、腎機能のモニタリングも有用と考えられる。高齢者では腎機能に応じて用量を調節すること［「用法・用量」及び「臨床薬理」の項（添付文書原文）参照］。

腎機能障害患者

血液透析中の末期腎不全患者を含む CL_{CR} 50 mL/min 未満の患者では用量調節が必要である［「用法・用量」、「警告及び使用上の注意」及び「臨床薬理」の項（添付文書原文）参照］。

過量投与

過量投与の場合は ZERBAXA の投与を中止し、対症療法を行うこと。ZERBAXA は血液透析により除去することができる。Ceftolozane の約66%、tazobactam の約56%、tazobactam 代謝物 M1の約51%が血液透析により除去された。過量投与の処置として血液透析が実施されたという情報は得られていない。

1.6.2.1.2　　EU 添付文書の概要（和訳）

販売名／販売会社名

販　売　名： Zerbaxa 1 g/0.5 g 点滴用濃縮液用粉末製剤

販売会社名： Merck Sharp & Dohme Ltd.

剤型・含量

点滴用濃縮液用粉末（濃縮液用粉末）

白色～帯黄色の粉末。

1バイアル中、ceftolozane sulfate（ceftolozane として1 g）及び tazobactam sodium（tazobactam として0.5 g）を含有する。

10 mL の希釈液で溶解後のバイアル中の総容量は11.4 mL で、88 mg/mL の ceftolozane 及び 44 mg/mL の tazobactam を含有する。

1バイアル中、ナトリウム10 mmol（230 mg）を含有する。粉末を9 mg/mL（0.9%）注射用生理食塩液10 mL で溶解した時、バイアルはナトリウム11.5 mmol（265 mg）を含有する。

他の添加剤としてアルギニン及び無水クエン酸を含有する。

効能・効果

本剤は成人において以下の感染症に対する適応を有する：

複雑性腹腔内感染症

急性腎盂腎炎

複雑性尿路感染症

人工呼吸器関連肺炎を含む院内肺炎

抗菌薬の適正使用については、公式ガイダンスを考慮すること。

用法・用量

クレアチニン・クリアランス>50 mL/min の患者における推奨静脈内投与方法は、感染症の種類によって[表 1.6.2-7]に示すとおりである。

表 1.6.2-7　　クレアチニン・クリアランス>50 mL/min の患者における静脈内投与方法（感染症別）

感染症の種類	投与量	投与間隔	投与時間	投与期間
複雑性腹腔内感染症†	ceftolozane 1 g/tazobactam 0.5 g	8時間ごと	1時間	4～14日間
複雑性尿路感染症 急性腎盂腎炎	ceftolozane 1 g/tazobactam 0.5 g	8時間ごと	1時間	7日間
人工呼吸器関連肺炎を含む院内肺炎‡	ceftolozane 2 g/tazobactam 1 g	8時間ごと	1時間	8～14日間

†嫌気性病原菌が疑われる場合は、メトロニダゾールを併用すること。
‡グラム陽性病原菌が感染過程に関与している又は関与が疑われる場合、グラム陽性菌に対する抗菌薬を使用すること。

特殊集団

高齢者（65歳以上）

年齢のみを理由とした本剤の用量調節は不要である。

腎機能障害患者

軽度の腎機能障害患者（推定クレアチニン・クリアランス>50 mL/min）には本剤の用量調節は不要である。中等度又は重度の腎機能障害患者及び血液透析中の末期腎不全患者では[表 1.6.2-8]のとおり用量調節を行うこと。

表 1.6.2-8　　クレアチニン・クリアランス≤50 mL/min の患者における推奨静脈内投与方法

推定クレアチニン・クリアランス（mL/min）†	複雑性腹腔内感染症、複雑性尿路感染症、急性腎盂腎炎‡	人工呼吸器関連肺炎を含む院内肺炎‡
30～50	Ceftolozane 500 mg/tazobactam 250 mg 静注 8時間ごと	Ceftolozane 1 g/tazobactam 0.5 g 静注 8時間ごと
15～29	Ceftolozane 250 mg/tazobactam 125 mg 静注 8時間ごと	Ceftolozane 500 mg/tazobactam 250 mg 静注 8時間ごと
血液透析中の末期腎不全	Ceftolozane 500 mg/tazobactam 250 mg を単回投与し、その後は維持用量として Ceftolozane 100 mg /tazobactam 50 mg を8時間ごとに投与（血液透析の日には、血液透析完了後できるだけ速やかに投与すること）。	Ceftolozane 1.5 g/tazobactam 0.75 g を単回投与し、その後は維持用量として Ceftolozane 300 mg/tazobactam 150 mg を8時間ごとに投与（血液透析の日には、血液透析完了後できるだけ速やかに投与すること）。

†クレアチニン・クリアランスは Cockcroft-Gault 式を使って推定した。
‡本剤のすべての投与は1時間かけての静脈内投与であり、すべての適応症に推奨される。投与期間は[表 1.6.2-6]の推奨に従うこと。

肝機能障害患者

肝機能障害患者での用量調節は不要である。

小児への投与

小児及び18歳未満の未成年者における ceftolozane/tazobactam の安全性及び有効性は確立されていない。データがない。

投与方法

本剤は点滴静脈内投与用である。

点滴静脈内投与時間は本剤すべての用量で1時間である。

適用上の注意

本剤を他の薬剤と混和しないこと。

バイアルは単回投与用である。

本剤の注射液は無菌的に調製すること。

調製方法

各バイアルに注射用水又は0.9%注射用生理食塩液10 mL を加えて緩やかに振盪し、溶解液を調製する。溶解後の液量は各バイアル約11.4 mL となる。濃度は各バイアル約132 mg/mL（88 mg/mL ceftolozane 及び44 mg/mL tazobactam）である。

注意：溶解液を直接投与しないこと。

Ceftolozane 2 g/tazobactam 1 g の用量の注射液を調製する際は、シリンジを用いて2つのバイアル（各バイアル約11.4 mL）から全量を抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 1.5 g/tazobactam 0.75 g の用量の注射液を調製する際は、シリンジを用いて1本目のバイアル（各バイアル約11.4 mL）から全量を、2本目のバイアルから5.7 mL を抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 1 g/tazobactam 0.5 g の用量の注射液を調製する際は、全量（約11.4 mL）をシリンジを用いてバイアルから抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 500 mg/tazobactam 250 mg の用量の注射液を調製する際は、5.7 mL をバイアルから抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 300 mg/tazobactam 150 mg の用量の注射液を調製する際は、3.5 mL をバイアルから抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 250 mg/tazobactam 125 mg の用量の注射液を調製する際は、2.9 mL をバイアルから抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

Ceftolozane 100 mg/tazobactam 50 mg の用量の注射液を調製する際は、1.2 mL をバイアルから抜き取り、0.9%注射用生理食塩液又は5%ブドウ糖注射液100 mL の入った輸液バッグに加える。

本剤注射液は無色～微黄色の澄明な液体である。色がこの範囲内であれば力価に影響はない。
有効成分の1つであるセフトロザンは、水生環境に到達すると有害な影響を及ぼす可能性がある。未使用の医薬品又は廃棄物質を廃水などを介して廃棄しないこと。未使用の医薬品又は廃棄物質は、当該地域の処分方法に従うこと。環境保護のため上記の指示を守ること。

禁忌

・本剤の有効成分又は添加剤に対し過敏症の既往歴のある患者
・セファロスポリン系の抗菌薬に対し過敏症の既往歴がある患者
・他の β-ラクタム系抗菌薬（ペニシリン系、カルバペネム系など）に対する重度の過敏症（アナフィラキシー反応、重度の皮膚反応など）の既往歴のある患者

警告及び使用上の注意

過敏症反応：

重篤でまれに致死的な過敏症（アナフィラキシー）反応を起こす可能性がある。Ceftolozane/tazobactam 投与中に重度のアレルギー反応が起きた場合は、投与を中止し適切な処置を行うこと。

セファロスポリン系、ペニシリン系、又は他の β-ラクタム系の抗菌薬に対し過敏症の既往歴のある患者は、ceftolozane/tazobactam にも過敏症を起こす可能性がある。

Ceftolozane/tazobactam は ceftolozane、tazobactam、又はセファロスポリンに過敏症の既往歴のある患者には禁忌である。

Ceftolozane/tazobactam はまた、他の β-ラクタム系抗菌薬（ペニシリン系、カルバペネム系など）に対し重度の過敏症（アナフィラキシー反応、重度の皮膚反応など）のある患者に禁忌である。

Ceftolozane/tazobactam はペニシリン系や他の β-ラクタム系抗菌薬に対し過敏症の既往歴のある患者には慎重に投与すること。

腎機能への影響：

Ceftolozane/tazobactam を投与された患者に腎機能の低下がみられた。

腎機能障害：

Ceftolozane/tazobactam の用量は、腎機能障害の程度に応じて調節する（「用法・用量」の項（添付文書原文）参照）。

複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症の臨床試験では、ベースライン時に腎機能障害の程度が中等度の患者は、正常又は軽度の患者と比較して臨床的治癒率が低かった。ベースライン時に腎機能障害が認められた患者は、投与期間中は腎機能の変動について頻回にモニタリングし、必要に応じ ceftolozane/tazobactam の用量を調節すること。

臨床データの限界：

免疫不全患者、重度の好中球減少症患者及び血液透析中の末期腎疾患患者は臨床試験から除外されている。

複雑性腹腔内感染症：

複雑性腹腔内感染症患者の試験において、最も多い診断は虫垂穿孔又は虫垂周囲膿瘍［420/970例（43.3%）］で、そのうち137/420例（32.6%）はベースライン時にびまん性腹膜炎を有していた。全被験者の約82%が APACHE II (Acute Physiology and Chronic Health Evaluation II) スコア<10で、2.3%がベースライン時に菌血症を有していた。臨床評価可能集団において、ceftolozane/tazobactam の臨床治癒率は65歳未満の293例で95.9%、65歳以上の82例で87.8%であった。

複雑性尿路感染症：

複雑性下部尿路感染症患者での臨床効果についてのデータは限られている。無作為化実薬対照試験では、細菌学的評価が可能な（ME）患者の18.2%（126/693例）が複雑性下部尿路感染症を合併しており、60/126例が ceftolozane/tazobactam を投与された。60例のうち1例はベースライン時に菌血症を有していた。

C. difficile 関連下痢症：

Ceftolozane/tazobactam で、抗菌薬関連の大腸炎や偽膜性大腸炎が報告されている（「副作用」の項（添付文書原文）参照）。これらの感染症の程度は軽度から生命を脅かすものまで様々である。したがって、ceftolozane/tazobactam 投与中又は投与後に下痢がみられた患者にこの診断を考慮することが重要である。そのような場合、ceftolozane/tazobactam の投与中止、及び対症療法と *C. difficile* に対する抗菌薬投与を検討すること。

薬剤耐性菌：

Ceftolozane/tazobactam の使用は、薬剤耐性菌の過剰な増殖を誘発する可能性がある。Ceftolozane/tazobactam 投与中又は投与後に重複感染が発現した場合、適切な処置を行うこと。

Ceftolozane/tazobactam は、tazobactam で阻害されない β-ラクタマーゼの産生菌に対して抗菌活性を有さない。

直接抗グロブリン試験（クームス試験）セロコンバージョン及び溶血性貧血の潜在的リスク：

Ceftolozane/tazobactam の投与中は、直接抗グロブリン試験が陽性となることがある。臨床試験では、ceftolozane/tazobactam 投与中に直接抗グロブリン試験が陽性となった患者が溶血性貧血であることを裏付けるものはなかった。

ナトリウム含量：

Ceftolozane/tazobactam はバイアル中230 mg のナトリウムを含有し、これは成人に対して WHO が推奨する1日最大摂取量の2 g のナトリウムの11.5%に相当する。0.9%注射用生理食塩液10 mL で溶解後のバイアルは265 mg のナトリウムを含有し、これは成人に対して WHO が推奨する1日最大摂取量である2 g のナトリウムの13.3%に相当する。

<u>薬物相互作用</u>

In vitro 及び *in vivo* 試験の結果からは、ceftolozane/tazobactam は、チトクロム P450（CYP）の基質、CYP 阻害薬及び CYP 誘導薬と臨床的に意味のある薬物間相互作用を示さないと考えられる。

In vitro では、ceftolozane、tazobactam 及び tazobactam の M1代謝物は、治療域の血漿中薬物濃度で、CYP1A2、CYP2B6、CYP2C8、CYP2C9、CYP2C19、CYP2D6又は CYP3A4に対する阻害作用は認められず、CYP1A2、CYP2B6又は CYP3A4に対する誘導作用も認められなかった。

In vitro では、治療域の血漿中薬物濃度において、ceftolozane 及び tazobactam は、P-糖蛋白質（P-gp）又は乳癌耐性蛋白質（BCRP）の基質ではなく、tazobactam は有機カチオントランスポーター（OCT）2の基質ではなかった。また、ceftolozane は P-gp、BCRP、有機アニオン輸送ポリペプチド（OATP）1B1、OATP1B3、OCT1、OCT2、多剤耐性関連蛋白（MRP）、胆汁酸トランスポーター（BSEP）、OAT1、OAT3、multidrug and toxin extrusion（MATE）1及び MATE2-K に対する阻害作用を示さなかった。また、tazobactam 及び tazobactam の M1代謝物のどちらも *in vitro* では治療域の血漿中薬物濃度において P-gp、BCRP、OATP1B1、OATP1B3、OCT1、OCT2又は BSEP に対する阻害作用を示さなかった。

Tazobactam は、OAT1及び OAT3の基質である。Tazobactam は、*in vitro* でヒト OAT1及び OAT3 を阻害し、50%阻害濃度（IC_{50}）値はそれぞれ 118 µg/mL 及び 147 µg/mL であった。Ceftolozane/tazobactam と OAT1及び OAT3の基質のフロセミドを併用した臨床試験では、フロセミドの血漿中濃度の有意な上昇は認められなかった（幾何平均比 C_{max} 0.83、AUC 0.87）。しかしながら、OAT1又は OAT3の阻害薬（プロベネシド等）を併用すると、tazobactam の血漿中濃度が上昇することがある。

<u>生殖可能な男女、妊婦及び授乳婦</u>

妊婦：

妊娠中の婦人への ceftolozane/tazobactam の投与に関するデータは得られていない。Tazobactam は胎盤を通過する。Ceftolozane が胎盤を通過するかは不明である。

Tazobactam の動物試験では、生殖毒性が認められたが、催奇形性は認められなかった。Ceftolozane のマウス及びラットの動物試験では、生殖毒性又は催奇形性は認められなかった。妊娠及び授乳期のラットに ceftolozane を投与したところ、生後60日の雄出生児に聴覚性驚愕反応の低下が認められた。

妊娠中は、有益性が妊婦と胎児に与える危険性を上回る場合にのみ本剤を投与すること。

授乳婦：
Ceftolozane 及び tazobactam がヒト乳汁中へ移行するかは不明である。新生児又は乳児に対するリスクは排除できない。乳児への授乳の有益性と母親の治療上の有益性を勘案し、本剤の投与を中止又は中断するか、授乳を中止すること。

生殖可能な男女：
Ceftolozane 及び tazobactam のヒトの受胎能への影響については検討されていない。Tazobactam を腹腔内投与又は ceftolozane を静注内投与したラットの受胎能試験では、受胎能や交尾への影響は認められなかった。

運転及び機械操作への影響
本剤は、運転及び機械操作への影響はわずかである。本剤投与後に浮動性めまいが起きることがある（「副作用」の項（添付文書原文）参照）。

副作用
安全性プロファイルの概要：
複雑性尿路感染症（腎盂腎炎を含む）及び複雑性腹腔内感染症の患者1,015例を対象とした実薬対照第Ⅲ相試験において、本剤（8時間ごとに ceftolozane 1 g/tazobactam 0.5 g 静脈内投与、腎機能障害患者の場合は適宜調節）を最長14日間投与して評価した。

もっともよくみられた副作用（複雑性腹腔内感染症及び腎盂腎炎を含む複雑性尿路感染症の第Ⅲ相試験統合解析で発現頻度3%以上）は悪心、頭痛、便秘、下痢及び発熱で、程度は概して軽度又は中等度であった。

本剤は、人工呼吸器関連肺炎を含む院内肺炎の第Ⅲ相比較対照臨床試験で評価された。臨床試験では、計361例に、本剤を最長14日間（ceftolozane 2 g/tazobactam 1 g を8時間ごとに静脈内投与、腎機能に応じて適宜調整）投与した。

もっともよくみられた副作用（人工呼吸器関連肺炎を含む院内肺炎の第Ⅲ相試験で発現頻度5%以上）は、下痢、アラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加であり、程度は概して軽度又は中等度であった。

複雑性腹腔内感染症、腎盂腎炎を含む複雑性尿路感染症及び人工呼吸器関連肺炎を含む院内肺炎の副作用一覧表

副作用の一覧：

臨床試験で認められた本剤の副作用を下表に示す。副作用はMedDRAの器官別大分類別及び発現頻度別に分類して示した。発現頻度は「よくみられる（≧1/100～<1/10）」と「まれな（≧1/1,000～<1/100）」で示した（[表 1.6.2-9]参照）。

表 1.6.2-9　　臨床試験で認められた ceftolozane/tazobactam の副作用

器官別大分類	よくみられる （≧1/100～<1/10）	まれな （≧1/1,000～<1/100）
感染症および寄生虫症	クロストリジウム・ディフィシレ大腸炎[2]	中咽頭及び外陰部腟カンジダ症[1]、クロストリジウム・ディフィシレ大腸炎[1]、真菌性尿路感染[1]、クロストリジウム・ディフィシレ感染症[2]
血液およびリンパ系障害	血小板増加症[1]	貧血[1]
代謝および栄養障害	低カリウム血症[1]	高血糖[1]、低マグネシウム血症[1]、低リン酸血症[1]
精神障害	不眠症[1]、不安[1]	-
神経系障害	頭痛[1]、浮動性めまい[1]	虚血性脳卒中[1]
心臓障害	-	心房細動[1]、頻脈[1]、狭心症[1]
血管障害	低血圧[1]	静脈炎[1]、静脈血栓症[1]
呼吸器、胸郭および縦隔障害	-	呼吸困難[1]
胃腸障害	悪心[1]、下痢[3]、便秘[1]、嘔吐[3]、腹痛[1]	胃炎[1]、腹部膨満[1]、消化不良[1]、鼓腸[1]、麻痺性イレウス[1]
皮膚および皮下組織障害	発疹[1]	蕁麻疹[1]
腎および尿路障害	-	腎機能障害[1]、腎不全[1]
一般・全身障害および投与部位の状態	発熱[1]、注入部位反応[1]	-
臨床検査	アラニンアミノトランスフェラーゼ増加[3]、アスパラギン酸アミノトランスフェラーゼ増加[3]、トランスアミナーゼ上昇[2]、肝機能検査異常[2]、血中アルカリホスファターゼ増加[2]、γ-グルタミルトランスフェラーゼ増加[2]	クームス試験陽性[3]、血清 γ-グルタミルトランスペプチダーゼ増加[1]、血清アルカリホスファターゼ増加[1]、クロストリジウム検査陽性[2]

1　複雑性腹腔内感染症、急性腎盂腎炎及び複雑性尿路感染症患者に Zerbaxa（1 g/0.5 g を8時間ごとに静脈内投与）を最長14日間投与した場合に特異的に認められた事象。
2　人工呼吸器関連肺炎を含む院内肺炎患者に Zerbaxa（2 g/1 g を8時間ごとに静脈内投与）を最長14日間投与した場合に特異的に認められた事象。
3　複雑性腹腔内感染症、急性腎盂腎炎、複雑性尿路感染症及び人工呼吸器関連肺炎を含む院内肺炎のすべての患者に認められた事象。

特定の副作用の詳細：

臨床検査値

Zerbaxa の投与中は、直接クームス試験で陽性となることがある。複雑性腹腔内感染症患者及び複雑性尿路感染症患者を対象とした臨床試験では、直接クームス試験でのセロコンバージョンの発現頻度は、Zerbaxa 群0.2%、対照群0%であった。人工呼吸器関連肺炎を含む院内肺炎患者を対象とした臨床試験では、直接クームス試験でのセロコンバージョンの発現頻度は、Zerbaxa 群31.2%、メロペネム群3.6%であった。臨床試験では、いずれの投与群においても直接クームス試験が陽性となった患者で溶血が発現したことを裏付けるものはみられなかった。

副作用の疑い（Suspected adverse reactions）の報告：

医薬品承認後に副作用の疑いを報告することは重要である。それにより、医薬品のリスク／ベネフィットバランスの継続的なモニタリングが可能となる。医療従事者は、Appendix V で示す国の報告システムを介して副作用の疑いを報告するよう求められる。

過量投与

本剤での過量投与の経験はない。臨床試験で投与された1回あたりの最高用量は、健康被験者に投与された ceftolozane 3 g/tazobactam 1.5 g であった。

過量投与の場合は本剤の投与を中止し、対症療法を行うこと。本剤は血液透析により除去することができる。血液透析により ceftolozane の約66%、tazobactam の約56%、tazobactam の代謝物M1の約51%が除去された。

1.6.2.2　　外国の添付文書（原文）

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZERBAXA safely and effectively. See full prescribing information for ZERBAXA.

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage	
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1.3)	6/2019
Dosage and Administration (2)	6/2019

----------INDICATIONS AND USAGE----------

ZERBAXA (ceftolozane and tazobactam) is a combination of ceftolozane, a cephalosporin antibacterial, and tazobactam, a beta-lactamase inhibitor, indicated in patients 18 years or older for the treatment of the following infections caused by designated suscept ble microorganisms:

- Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole (1.1)
- Complicated Urinary Tract Infections (cUTI), Including Pyelonephritis (1.2)
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1.3)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer all doses of ZERBAXA every 8 hours by intravenous infusion over 1 hour in patients 18 years or older. (2.1, 2.2)
- See Full Prescr bing Information for instructions on the preparation of solutions. (2.3)
- For doses above 1.5 g, reconstitute a second vial in the same manner as the first one, withdraw an appropriate volume (per Table 3 in the Full Prescr bing Information), and add to the same infusion bag. (2.3)

Recommended Dosage of ZERBAXA by Infection in Patients 18 years or older with Creatinine Clearance (CrCl) Greater than 50 mL/min (2.1)

Infection	Dose	Duration of Treatment
Complicated Intra-abdominal Infections (cIAI)*	1.5 g	4-14 days
Complicated Urinary Tract Infections (cUTI), Including Pyelonephritis	1.5 g	7 days
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	3 g	8-14 days

* Used in conjunction with metronidazole 500 mg intravenously every 8 hours

Recommended Dosage of ZERBAXA in Patients 18 years or older with CrCl 50 mL/min or less (2.2)

Estimated CrCl (mL/min)*	cIAI and cUTI, including pyelonephritis	HABP/VABP
30 to 50	ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours	ZERBAXA 1.5 g (1 g and 0.5 g) intravenously every 8 hours
15 to 29	ZERBAXA 375 mg (250 mg and 125 mg) intravenously every 8 hours	ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ZERBAXA 750 mg (500 mg and 250 mg) followed by a ZERBAXA 150 mg (100 mg and 50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest poss ble time following completion of dialysis)	A single loading dose of ZERBAXA 2.25 g (1.5 g and 0.75 g) followed by a ZERBAXA 450 mg (300 mg and 150 mg) maintenance dose administered every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

* CrCl estimated using Cockcroft-Gault formula

---------- DOSAGE FORMS AND STRENGTHS ----------

- ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection supplied as a sterile powder for reconstitution in single-dose vials containing ceftolozane 1 g (equivalent to 1.147 g ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g tazobactam sodium). (3)

----------CONTRAINDICATIONS----------

- ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Decreased efficacy was observed in a Phase 3 cIAI trial in a subgroup of patients with baseline CrCl of 30 to ≤50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly. (5.1)
- Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibacterial drugs. Exercise caution in patients with known hypersensitivity to beta-lactam antibacterial drugs. If an anaphylactic reaction to ZERBAXA occurs, discontinue the drug and institute appropriate therapy. (5.2)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including ZERBAXA. Evaluate if diarrhea occurs. (5.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥5% in either cIAI or cUTI indication) are nausea, diarrhea, headache and pyrexia. The most common adverse reactions (≥5% in the HABP/VABP indication) are increase in hepatic transaminases, renal impairment/renal failure, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Geriatrics: Higher incidence of adverse reactions was observed in patients aged 65 years and older. In a Phase 3 cIAI trial, cure rates were lower in patients 65 years and older. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Complicated Intra-abdominal Infections

ZERBAXA used in combination with metronidazole is indicated for the treatment of patients 18 years and older with complicated intra-abdominal infections (cIAI) caused by the following susceptible Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus salivarius*.

1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

ZERBAXA is indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

1.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

ZERBAXA is indicated for the treatment of patients 18 years and older with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

1.4 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ZERBAXA for injection is 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g) for cIAI and cUTI and 3 g (ceftolozane 2 g and tazobactam 1 g) for HABP/VABP administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older and with a creatinine clearance (CrCl) greater than 50 mL/min. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress as shown in Table 1.

Table 1: Dosage of ZERBAXA by Infection in Patients with CrCl Greater than 50 mL/min

Infection	Dose	Frequency	Infusion Time (hours)	Duration of Treatment
Complicated Intra-abdominal Infections*	1.5 g	Every 8 Hours	1	4-14 days
Complicated Urinary Tract	1.5 g	Every 8 Hours	1	7 days

Infections, Including Pyelonephritis				
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	3 g	Every 8 Hours	1	8-14 days

* Used in conjunction with metronidazole 500 mg intravenously every 8 hours

2.2 Dosage Adjustments in Patients with Renal Impairment

Dose adjustment is required for patients with CrCl 50 mL/min or less (Table 2). All doses of ZERBAXA are administered over 1 hour. For patients with changing renal function, monitor CrCl at least daily and adjust the dosage of ZERBAXA accordingly *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Table 2: Dosage of ZERBAXA in Adult Patients with CrCl 50 mL/min or less

Estimated CrCl (mL/min)*	**Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis**	**Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)**
30 to 50	750 mg (500 mg and 250 mg) intravenously every 8 hours	1.5 g (1 g and 0.5 g) intravenously every 8 hours
15 to 29	375 mg (250 mg and 125 mg) intravenously every 8 hours	750 mg (500 mg and 250 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 mg and 50 mg) maintenance dose administered every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)	A single loading dose of 2.25 g (1.5 g and 0.75 g) followed by a 450 mg (300 mg and 150 mg) maintenance dose administered every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

***** CrCl estimated using Cockcroft-Gault formula

2.3 Preparation of Solutions

ZERBAXA does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses:

Constitute each vial of ZERBAXA with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP and gently shake to dissolve. The final volume is approximately 11.4 mL per vial. Caution: The constituted solution is not for direct injection.

To prepare the required dose, withdraw the appropriate volume determined from Table 3 from the reconstituted vial(s). Add the withdrawn volume to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP. For doses above 1.5 g, reconstitute a second vial in the same manner as the first one, withdraw an appropriate volume (per Table 3), and add to the same infusion bag.

Table 3: Preparation of Doses

ZERBAXA (ceftolozane and tazobactam) Dose	Volume to Withdraw from Reconstituted Vial(s)
3 g (2 g and 1 g)	Two vials of 11.4 mL each (entire contents from two vials)
2.25 g (1.5 g and 0.75 g)	11.4 mL from one vial (entire contents) and 5.7 mL from a second vial
1.5 g (1 g and 0.5 g)	11.4 mL (entire contents from one vial)
750 mg (500 mg and 250 mg)	5.7 mL
450 mg (300 mg and 150 mg)	3.5 mL
375 mg (250 mg and 125 mg)	2.9 mL
150 mg (100 mg and 50 mg)	1.2 mL

Inspect drug products visually for particulate matter and discoloration prior to use. ZERBAXA infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

2.4 Compatibility

Compatibility of ZERBAXA with other drugs has not been established. ZERBAXA should not be mixed with other drugs or physically added to solutions containing other drugs.

2.5 Storage of Constituted Solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride injection, reconstituted ZERBAXA solution may be held for 1 hour prior to transfer and dilution in a suitable infusion bag.

Following dilution of the solution with 0.9% sodium chloride or 5% dextrose, ZERBAXA is stable for 24 hours when stored at room temperature or 7 days when stored under refrigeration at 2 to 8°C (36 to 46°F).

Constituted ZERBAXA solution or diluted ZERBAXA infusion should not be frozen.

3 DOSAGE FORMS AND STRENGTHS

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied as a white to yellow sterile powder for reconstitution in single-dose vials; each vial contains ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium).

4 CONTRAINDICATIONS

ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Efficacy in Patients with Baseline Creatinine Clearance of 30 to 50 mL/min

In a subgroup analysis of a Phase 3 cIAI trial, clinical cure rates were lower in patients with baseline CrCl of 30 to 50 mL/min compared to those with CrCl greater than 50 mL/min (Table 4). The reduction in clinical cure rates was more marked in the ZERBAXA plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of ZERBAXA accordingly *[see Dosage and Administration (2.2)]*.

Table 4: Clinical Cure Rates in a Phase 3 Trial of cIAI by Baseline Renal Function (MITT Population)

Baseline Renal Function	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
CrCl greater than 50 mL/min	312/366 (85.2)	355/404 (87.9)
CrCl 30 to 50 mL/min	11/23 (47.8)	9/13 (69.2)

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.

Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product is to be given to a patient with a cephalosporin, penicillin, or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA occurs, discontinue the drug and institute appropriate therapy.

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is confirmed, discontinue antibacterials not directed against *C. difficile*, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

5.4 Development of Drug-Resistant Bacteria

Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious reactions are described in greater detail in the Warnings and Precautions section:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and also may not reflect rates observed in practice.

Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis

ZERBAXA was evaluated in Phase 3 comparator-controlled clinical trials of cIAI and cUTI, which included a total of 1015 patients treated with ZERBAXA (1.5 g every 8 hours, adjusted based on renal function where appropriate) and 1032 patients treated with comparator (levofloxacin 750 mg daily in cUTI or meropenem 1 g every 8 hours in cIAI) for up to 14 days. The mean age of treated patients was 48 to 50 years (range 18 to 92 years), across treatment arms and indications. In both indications, about 25% of the subjects were 65 years of age or older. Most patients (75%) enrolled in the cUTI trial were female, and most patients (58%) enrolled in the cIAI trial were male. Most patients (>70%) in both trials were enrolled in Eastern Europe and were White.

The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA were nausea, diarrhea, headache, and pyrexia. Table 5 lists adverse reactions occurring in 1% or greater of patients receiving ZERBAXA in Phase 3 cIAI and cUTI clinical trials.

Table 5: Adverse Reactions Occurring in 1% or Greater of Patients Receiving ZERBAXA in Phase 3 cIAI and cUTI Clinical Trials

Preferred Term	Complicated Intra-abdominal Infections		Complicated Urinary Tract Infections, Including Pyelonephritis	
	ZERBAXA* (N=482) n (%)	Meropenem (N=497) n (%)	ZERBAXA* (N=533) n (%)	Levofloxacin (N=535) n (%)
Nausea	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
Headache	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
Diarrhea	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
Pyrexia	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
Constipation	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
Insomnia	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)
Vomiting	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
Hypokalemia	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
ALT increased	7 (1.5)	5 (1)	9 (1.7)	5 (0.9)
AST increased	5 (1)	3 (0.6)	9 (1.7)	5 (0.9)
Anemia	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
Thrombocytosis	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
Abdominal pain	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
Anxiety	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
Dizziness	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
Hypotension	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)
Atrial fibrillation	6 (1.2)	3 (0.6)	1 (0.2)	0
Rash	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)

* The ZERBAXA for injection dose was 1.5 g intravenously every 8 hours, adjusted to match renal function where appropriate. In the cIAI trials, ZERBAXA was given in conjunction with metronidazole.

Treatment discontinuation due to adverse events occurred in 2.0% (20/1015) of patients receiving ZERBAXA and 1.9% (20/1032) of patients receiving comparator drugs. Renal impairment (including the terms renal impairment, renal failure, and renal failure acute) led to discontinuation of treatment in 5/1015 (0.5%) subjects receiving ZERBAXA and none in the comparator arms.

Increased Mortality

In the cIAI trials (Phase 2 and 3), death occurred in 2.5% (14/564) of patients receiving ZERBAXA and in 1.5% (8/536) of patients receiving meropenem. The causes of death varied and included worsening and/or complications of infection, surgery and underlying conditions.

Less Common Adverse Reactions in Phase 3 cIAI and cUTI Clinical Trials

The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 1%:

Cardiac disorders: tachycardia, angina pectoris

Gastrointestinal disorders: gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic

General disorders and administration site conditions: infusion site reactions

Infections and infestations: candidiasis including oropharyngeal and vulvovaginal, fungal urinary tract infection
Investigations: increased serum gamma-glutamyl transpeptidase (GGT), increased serum alkaline phosphatase, positive Coombs test
Metabolism and nutrition disorders: hyperglycemia, hypomagnesemia, hypophosphatemia
Nervous system disorders: ischemic stroke
Renal and urinary system: renal impairment, renal failure
Respiratory, thoracic and mediastinal disorders: dyspnea
Skin and subcutaneous tissue disorders: urticaria
Vascular disorders: venous thrombosis

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

ZERBAXA was evaluated in a Phase 3 comparator-controlled clinical trial for HABP/VABP, which included a total of 361 patients treated with ZERBAXA (3 g every 8 hours, adjusted based on renal function where appropriate) and 359 patients treated with comparator (meropenem 1 g every 8 hours) for up to 14 days. The mean age of treated patients was 60 years (range 18 to 98 years), across treatment arms. About 44% of the subjects were 65 years of age or older. Most patients (71%) enrolled in the trial were male. All subjects were mechanically ventilated at randomization and 92% were in an intensive care unit (ICU) at randomization. The median APACHE II score was 17, and 33% of subjects had a baseline APACHE II score of ≥20, indicating a high severity of illness for many patients enrolled in this trial.

Table 6 lists adverse reactions occurring in 2% or greater of patients receiving ZERBAXA in a Phase 3 HABP/VABP clinical trial.

Table 6: Adverse Reactions Occurring in 2% or Greater of Patients Receiving ZERBAXA in a Phase 3 HABP/VABP Clinical Trial

Adverse Reactions	ZERBAXA* N=361 n (%)	Meropenem N=359 n (%)
Hepatic transaminase increased[1]	43 (11.9)	26 (7.2)
Renal impairment/renal failure[2]	32 (8.9)	22 (6.1)
Diarrhea	23 (6.4)	25 (7.0)
Intracranial hemorrhage[3]	16 (4.4)	5 (1.4)
Vomiting	12 (3.3)	10 (2.8)
Clostridium difficile colitis[4]	10 (2.8)	2 (0.6)

* The ZERBAXA for injection dose was 3 g intravenously every 8 hours, adjusted to match renal function where appropriate.
[1] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal.
[2] Includes acute renal failure, anuria, azotemia, oliguria, prerenal failure, renal failure, renal impairment.
[3] Includes cerebellar hemorrhage, cerebral hematoma, cerebral hemorrhage, hemorrhage intracranial, hemorrhagic stroke, hemorrhagic transformation stroke, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma.
[4] Includes *Clostridium difficile* colitis*, Clostridium difficile* infection, *Clostridium* test positive*.*

Treatment discontinuation due to adverse reactions occurred in 1.1% (4/361) of patients receiving ZERBAXA and 1.4% (5/359) of patients receiving meropenem.

Less Common Adverse Reactions in a Phase 3 HABP/VABP Clinical Trial
The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 2%:

Investigations: blood alkaline phosphatase increased, gamma-glutamyltransferase increased, Coombs direct test positive

Laboratory Values

The development of a positive direct Coombs test may occur during treatment with ZERBAXA. The incidence of seroconversion to a positive direct Coombs test was 0.2% in patients receiving ZERBAXA and 0% in patients receiving the comparator in the cUTI and cIAI clinical trials. The incidence of seroconversion to a positive direct Coombs test was 31.2% in patients receiving ZERBAXA and 3.6% in patients receiving meropenem in the HABP/VABP clinical trial. In clinical trials, there was no evidence of hemolysis in patients who developed a positive direct Coombs test in any treatment group.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on ZERBAXA, ceftolozane or tazobactam use in pregnant women to allow assessment of a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal or fetal outcomes (see Data). Neither ceftolozane nor tazobactam produced embryo-fetal toxicity when administered to rodents during the period of organogenesis at ceftolozane doses approximately 3.5 times higher in mice and 2 times higher in rats than the maximum recommended human dose (MRHD) of 2 grams every 8 hours based on plasma AUC comparison or at tazobactam doses approximately 10 times higher in rats than the MRHD of 1 gram every 8 hours based on body surface area comparison. In pre-postnatal studies, where pregnant rats were administered intravenous ceftolozane or intraperitoneal tazobactam in gestation and through the lactation period, ceftolozane was associated with a decrease in auditory startle response in first generation offspring at a dose lower than the MRHD based on AUC comparison, and tazobactam was associated with reduced maternal body weight gain and increased still births at a dose equivalent to approximately 4 times the MRHD and reduced fetal body weights in first generation offspring at a dose approximately equivalent to the MRHD based on body surface area comparison (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

While available studies with multiple cephalosporins cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Ceftolozane

Embryo-fetal development studies were performed in mice administered intravenous ceftolozane at doses of 300, 1000, and 2000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 15) and in rats administered intravenous ceftolozane in doses of 100, 300, and 1000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 17). In mice ceftolozane was not associated with maternal or embryo-fetal toxicity with doses up to the highest dose of 2000 mg/kg/ day (approximately 3.5 times the MRHD of 2 grams every 8 hours based on plasma AUC comparison). In rats, no embryo-fetal toxicity was observed, but maternal body weight gain was reduced at a ceftolozane dose of 1000 mg/kg/day. No adverse maternal effects in rats were observed at a dose of 300 mg/kg/day and no

adverse embryo-fetal effects were observed at a dose of 1000 mg/kg/day (respectively equivalent to approximately 0.7- and 2-times the MRHD based on plasma AUC comparison).

In a pre-postnatal study in rats, intravenous ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal day 60 male pups at maternal doses greater than or equal to 300 mg/kg/day. No adverse effects were observed in rats at a dose of 100 mg/kg/day, a dose lower than the MRHD of 2 grams every 8 hours based on plasma AUC comparison.

Tazobactam

In an embryo-fetal study in rats, tazobactam was administered intravenously during the period of organogenesis (Gestation Day 7 through 17) at doses of 125, 500, and 3000 mg/kg/day. The high dose of 3000 mg/kg/day produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with fetal toxicity. No adverse maternal effects were observed at a dose of 500 mg/kg/day and no adverse fetal effects were observed at a dose of 3000 mg/kg/day (respectively equivalent to approximately 2- and 10-times the MRHD of 1 gram every 8 hours based on body surface area comparison). In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre-postnatal study in rats, tazobactam administered intraperitoneally in doses of 40, 320, and 1280 mg/kg/day at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) was associated with decreased maternal food consumption and body weight gain at the end of gestation and significantly more stillbirths at the high dose of 1280 mg/kg/day. No effects on the physical development, neurological function, or fertility and reproductive ability of first generation (F1) pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. The second generation (F2) fetuses were normal for all doses of tazobactam. No adverse effects on maternal reproduction were observed at doses up to 320 mg/kg/day and F1 body weights were not reduced at a dose of 40 mg/kg/day (respectively equivalent to approximately 1.0 and 0.1 times the MRHD of 1 gram every 8 hours based on body surface area comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of ceftolozane or tazobactam in human milk. There are no data on the effects of tazobactam or ceftolozane on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERBAXA and any potential adverse effects on the breastfed child from ZERBAXA or from the underlying maternal conditions.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1015 patients treated with ZERBAXA in the Phase 3 cIAI and cUTI clinical trials, 250 (24.6%) were 65 years or older, including 113 (11.1%) 75 years or older. The incidence of adverse events in both treatment groups was higher in older subjects (65 years or older) in the trials for both indications. In the cIAI trial, cure rates in the elderly (aged 65 years and older) in the ZERBAXA plus metronidazole arm were 69/100 (69%) and in the comparator arm were 70/85 (82.4%). This finding in the elderly population was not observed in the cUTI trial.

Of the 361 patients treated with ZERBAXA in the Phase 3 HABP/VABP clinical trial, 160 (44.3%) were 65 years or older, including 83 (23%) 75 years or older. The incidence of adverse events in both treatment groups was higher in older subjects (65 years or older). In the trial, Day 28 all-cause mortality rates in the elderly (aged 65 years and older) were comparable between treatment arms:50/160 (31.3%) in the ZERBAXA arm and 54/160 (33.8%) in the comparator arm.

ZERBAXA is substantially excreted by the kidney and the risk of adverse reactions to ZERBAXA may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. Adjust dosage for elderly patients based on renal function *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with CrCl 50 mL/min or less, including patients with ESRD on HD *[see Dosage and Administration (2.2), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

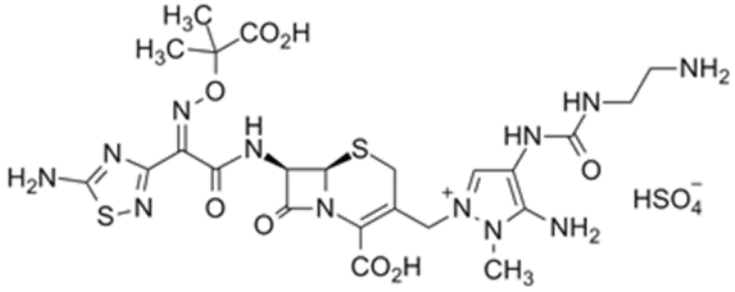
In the event of overdose, discontinue ZERBAXA and provide general supportive treatment. ZERBAXA can be removed by hemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the tazobactam metabolite M1 were removed by dialysis. No information is available on the use of hemodialysis to treat overdosage.

11 DESCRIPTION

ZERBAXA (ceftolozane and tazobactam) is an antibacterial combination product consisting of the cephalosporin antibacterial drug ceftolozane sulfate and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.

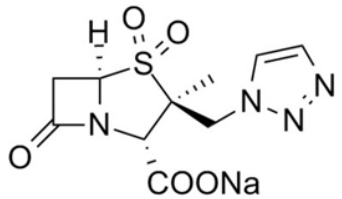
Ceftolozane sulfate is a semi-synthetic antibacterial drug of the beta-lactam class for parenteral administration. The chemical name of ceftolozane sulfate is 1*H*-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,sulfate (1:1). The molecular formula is $C_{23}H_{31}N_{12}O_8S_2^+ \bullet HSO_4^-$ and the molecular weight is 764.77.

Figure 1: Chemical structure of ceftolozane sulfate



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

Figure 2: Chemical structure of tazobactam sodium



ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is a white to yellow sterile powder for reconstitution consisting of ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium) per vial, packaged in single-dose glass vials. The product contains sodium chloride (487 mg/vial) as a stabilizing agent, citric acid (21 mg/vial), and L-arginine (approximately 600 mg/vial) as excipients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZERBAXA is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

As with other beta-lactam antibacterial agents, the percent time of dosing interval that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism has been shown to be the best predictor of efficacy in animal models of infection. The percent time of dosing interval that the plasma concentration of tazobactam exceeds a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in *in vitro* and *in vivo* models. The exposure-response analyses in efficacy and safety clinical trials for cIAI, cUTI, and HABP/VABP support the recommended dose regimens of ZERBAXA.

Cardiac Electrophysiology

In a randomized, positive and placebo-controlled crossover thorough QTc study, 51 healthy subjects were administered a single therapeutic dose of ZERBAXA 1.5 gram (ceftolozane 1 g and tazobactam 0.5 g) and a supratherapeutic dose of ZERBAXA 4.5 gram (ceftolozane 3 g and tazobactam 1.5 g). No significant effects of ZERBAXA on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected.

12.3 Pharmacokinetics

Ceftolozane and tazobactam pharmacokinetics are similar following single- and multiple-dose administrations. The C_{max} and AUC of ceftolozane and tazobactam increase in proportion to dose.

The mean steady-state population pharmacokinetic parameters of ZERBAXA in patients with cIAI and cUTI receiving 1-hour intravenous infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or patients with HABP/VABP receiving 1-hour intravenous infusions of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) every 8 hours are summarized in Table 7.

Table 7: Mean (SD) Steady-State Plasma Population Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) after Multiple Intravenous 1-hour Infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) Every 8 Hours in Patients with CrCl Greater than 50 mL/min

PK parameters	ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) in cIAI and cUTI Patients		ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) in HABP/VABP Patients	
	Ceftolozane (n=317)	Tazobactam (n=244)	Ceftolozane (n=247)	Tazobactam (n=247)
C_{max} (mcg/mL)	65.7 (27)	17.8 (9)	105 (46)	26.4 (13)
$AUC_{0\text{-}8,ss}$ (mcg•h/mL)	186 (74)	35.8 (57)	392 (236)	73.3 (76)

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is approximately 16% to 21% and 30%, respectively. The mean (CV%) steady-state volume of distribution of ZERBAXA in healthy adult males (n = 51) following a single intravenous dose of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) was 13.5 L (21%) and 18.2 L (25%) for ceftolozane and tazobactam, respectively, similar to extracellular fluid volume.

Following 1 hour intravenous infusions of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) or adjusted based on renal function every 8 hours in ventilated patients with confirmed or suspected pneumonia (N=22), mean pulmonary epithelial lining fluid-to-free plasma AUC ratios of ceftolozane and tazobactam were approximately 50% and 62%, respectively, and are similar to those in healthy subjects (approximately 61% and 63%, respectively) receiving ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g). Minimum ceftolozane and tazobactam epithelial lung lining fluid concentrations in ventilated subjects at the end of the dosing interval were 8.2 mcg/mL and 1.0 mcg/mL, respectively.

Elimination

Ceftolozane is eliminated from the body by renal excretion with a mean half-life of approximately 3 to 4 hours. Tazobactam is eliminated by renal excretion and metabolism with a plasma mean half-life of approximately 2 to 3 hours. The elimination half-life ($t_{1/2}$) of ceftolozane or tazobactam is independent of dose.

Metabolism

Ceftolozane does not appear to be metabolized to any appreciable extent and is not a substrate for CYP enzymes. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1.

Excretion

Ceftolozane, tazobactam and the tazobactam metabolite M1 are excreted by the kidneys. Following administration of a single ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) intravenous dose to healthy male adults, greater than 95% of ceftolozane was excreted in the urine as unchanged parent drug. More than 80% of tazobactam was excreted as the parent compound with the remainder excreted as the tazobactam M1 metabolite. After a single dose of ZERBAXA, renal clearance of ceftolozane (3.41 – 6.69 L/h) was similar to plasma CL (4.10 to 6.73 L/h) and similar to the glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is eliminated by the kidney via glomerular filtration. Tazobactam is a substrate for OAT1 and OAT3 transporters and its elimination has been shown to be inhibited by probenecid, an inhibitor of OAT1/3.

Specific Populations

Dose adjustment is not warranted on the basis of age (18 years and older), gender, or race/ethnicity. No significant differences in the pharmacokinetics of ceftolozane and tazobactam were observed based on age (18 years and older), gender, weight, or race/ethnicity.

Patients with Renal Impairment

The ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in subjects with CrCl 80-51 mL/min, 50-30 mL/min, and 29-15 mL/min, respectively, compared to healthy subjects with normal renal function. The respective tazobactam dose normalized geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required *[see Dosage and Administration (2.2)]*.

In subjects with ESRD on HD, approximately two-thirds of the administered ZERBAXA dose is removed by HD. A single loading dose of Zerbaxa followed by maintenance dose administered every 8 hours for the remainder of the treatment period is recommended in patients with ESRD on HD. On HD days, administer the dose at the earliest possible time following completion of HD. *[See Dosage and Administration (2.2).]*

Patients with Augmented Renal Function

Following a single 1 hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) to critically-ill patients with CrCl greater than or equal to 180 mL/min (N=10), mean terminal half-life values of ceftolozane and tazobactam were 2.6 hours and 1.5 hours, respectively. No dose adjustment of ZERBAXA is recommended for HABP/VABP patients with augmented renal function *[see Clinical Studies (14.3)]*.

Patients with Hepatic Impairment

As ZERBAXA does not undergo hepatic metabolism, the systemic clearance of ZERBAXA is not expected to be affected by hepatic impairment.

No dose adjustment is recommended for ZERBAXA in subjects with hepatic impairment.

Geriatric Patients

In a population pharmacokinetic analysis of ZERBAXA, no clinically relevant differences in exposure were observed with regard to age.

No dose adjustment of ZERBAXA based on age is recommended. Dosage adjustment for ZERBAXA in geriatric patients should be based on renal function *[see Dosage and Administration (2.2)]*.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Drug Interactions

No drug-drug interaction was observed between ceftolozane and tazobactam in a clinical study in 16 healthy subjects. *In vitro* and *in vivo* data indicate that ZERBAXA is unlikely to cause clinically relevant drug-drug interactions related to CYPs and transporters at therapeutic concentrations.

Drug Metabolizing Enzymes

In vivo data indicated that ZERBAXA is not a substrate for CYPs. Thus, clinically relevant drug-drug interactions involving inhibition or induction of CYPs by other drugs are unlikely to occur.

In vitro studies demonstrated that ceftolozane, tazobactam and the M1 metabolite of tazobactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations. *In vitro* induction studies in primary human hepatocytes demonstrated that ceftolozane, tazobactam, and the tazobactam metabolite M1 decreased CYP1A2 and CYP2B6 enzyme activity and mRNA levels in primary human hepatocytes as well as CYP3A4 mRNA levels at supratherapeutic plasma concentrations. Tazobactam metabolite M1 also decreased CYP3A4 activity at supratherapeutic plasma concentrations. A clinical drug-drug interaction study was conducted and results indicated drug interactions involving CYP1A2 and CYP3A4 inhibition by ZERBAXA are not anticipated.

Membrane Transporters

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic concentrations.

Tazobactam is a known substrate for OAT1 and OAT3. Co-administration of tazobactam with the OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71%. Co-administration of ZERBAXA with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam plasma concentrations.

In vitro data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K *in vitro* at therapeutic plasma concentrations.

In vitro data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. A clinical drug-drug interaction study was conducted and results indicated clinically relevant drug interactions involving OAT1/OAT3 inhibition by ZERBAXA are not anticipated.

12.4 Microbiology

Mechanism of Action

Ceftolozane belongs to the cephalosporin class of antibacterial drugs. The bactericidal action of ceftolozane results from inhibition of cell wall biosynthesis, and is mediated through binding to penicillin-binding proteins (PBPs). Ceftolozane is an inhibitor of PBPs of *P. aeruginosa* (e.g., PBP1b, PBP1c, and PBP3) and *E. coli* (e.g., PBP3).

Tazobactam sodium has little clinically relevant *in vitro* activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is an irreversible inhibitor of some beta-lactamases (e.g., certain penicillinases and cephalosporinases), and can bind covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases.

Resistance

Mechanisms of beta-lactam resistance may include the production of beta-lactamases, modification of PBPs by gene acquisition or target alteration, up-regulation of efflux pumps, and loss of outer membrane porin.

Clinical isolates may produce multiple beta-lactamases, express varying levels of beta-lactamases, or have amino acid sequence variations, and other resistance mechanisms that have not been identified.

Culture and susceptibility information and local epidemiology should be considered in selecting or modifying antibacterial therapy.

ZERBAXA demonstrated *in vitro* activity against Enterobacteriaceae in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, and OXA. ZERBAXA is not active against bacteria that produce serine carbapenemases [*K. pneumoniae* carbapenemase (KPC)], and metallo-beta-lactamases.

In ZERBAXA clinical trials, some isolates of Enterobacteriaceae with minimum inhibitory concentration to ZERBAXA of ≤2 mcg/mL produced beta-lactamases. These isolates produced one or more beta-lactamases of the following enzyme groups: CTX-M, OXA, TEM, or SHV.

Some of these beta-lactamases were also produced by isolates of Enterobacteriaceae with minimum inhibitory concentration to ZERBAXA >2 mcg/mL.

ZERBAXA demonstrated *in vitro* activity against *P. aeruginosa* isolates tested that had chromosomal AmpC, loss of outer membrane porin (OprD), or up regulation of efflux pumps (MexXY, MexAB).

Isolates resistant to other cephalosporins may be susceptible to ZERBAXA, although cross-resistance may occur.

Interaction with Other Antimicrobials

In vitro synergy studies suggest no antagonism between ZERBAXA and other antibacterial drugs (e.g., meropenem, amikacin, aztreonam, levofloxacin, tigecycline, rifampin, linezolid, daptomycin, vancomycin, and metronidazole).

Antimicrobial Activity

ZERBAXA has been shown to be active against the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Complicated Intra-abdominal Infections

Gram-negative bacteria:
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Gram-positive bacteria:
- *Streptococcus anginosus*
- *Streptococcus constellatus*
- *Streptococcus salivarius*

Anaerobic bacteria:
- *Bacteroides fragilis*

Complicated Urinary Tract Infections, Including Pyelonephritis

Gram-negative bacteria:
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Gram-negative bacteria:
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*

Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftolozane and tazobactam against isolates of similar genus or organism group. However, the efficacy of ZERBAXA in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria:
Citrobacter koseri
Klebsiella aerogenes
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia liquefaciens

Gram-positive bacteria:
Streptococcus agalactiae
Streptococcus intermedius

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for ceftolozane and tazobactam, please see:
https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an *in vitro* mouse lymphoma assay and an *in vivo* rat bone-marrow micronucleus assay. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, an *in vitro* mouse lymphoma assay, an *in vitro* HPRT assay in Chinese hamster ovary cells, an *in vivo* mouse micronucleus assay, and an *in vivo* unscheduled DNA synthesis (UDS) assay.

Tazobactam was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, an *in vitro* mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an *in vivo* mouse bone-marrow micronucleus assay, and an *in vivo* UDS assay.

Ceftolozane was administered in a fertility study at intravenous doses of 100, 300, and 1000 mg/kg/day to male rats for 28 days before mating and through the mating period and to female rats for 14 days before mating, through the mating period, and until the 7th day of gestation. Ceftolozane had no adverse effect on fertility in male or female rats at doses up to 1000 mg/kg/day (approximately 1.4 times the maximum recommended human dose (MHRD) of 2 grams every 8 hours based on AUC comparison).

In a rat fertility study, intraperitoneal tazobactam doses of 40, 160, and 640 mg/kg/day were administered twice-daily, to male rats beginning 70 days before mating and through the mating period, and to female rats beginning 14 days before mating, during the mating period, and until Gestation Day 21. Male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 2 times the MRHD of 1 gram every 8 hours based on body surface comparison).

14 CLINICAL STUDIES

14.1 Complicated Intra-abdominal Infections

A total of 979 adults hospitalized with cIAI were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) intravenously every 8 hours plus metronidazole (500 mg intravenously every 8 hours) to meropenem (1 g intravenously every 8 hours) for 4 to 14 days of therapy. Complicated intra-abdominal infections included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis. The majority of patients (75%) were from Eastern Europe; 6.3% were from the United States.

The primary efficacy endpoint was clinical response, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-cure (TOC) visit which occurred 24 to 32 days after the first dose of study drug. The primary efficacy analysis population was the microbiological intent-to-treat (MITT) population, which included all patients who had at least 1 baseline intra-abdominal pathogen regardless of the susceptibility to study drug. The key secondary efficacy endpoint was clinical response at the TOC visit in the microbiologically evaluable (ME) population, which included all protocol-adherent MITT patients.

The MITT population consisted of 806 patients; the median age was 52 years and 57.8% were male. The most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 47% of patients. Diffuse peritonitis at baseline was present in 34.2% of patients.

ZERBAXA plus metronidazole was non-inferior to meropenem with regard to clinical cure rates at the TOC visit in the MITT population. Clinical cure rates at the TOC visit are displayed by patient population in Table 8. Clinical cure rates at the TOC visit by pathogen in the MITT population are presented in Table 9.

Table 8: Clinical Cure Rates in a Phase 3 Trial of Complicated Intra-Abdominal Infections

Analysis Population	ZERBAXA plus metronidazole* n/N (%)	Meropenem† n/N (%)	Treatment Difference (95% CI)‡
MITT	323/389 (83)	364/417 (87.3)	-4.3 (-9.2, 0.7)
ME	259/275 (94.2)	304/321 (94.7)	-0.5 (-4.5, 3.2)

* ZERBAXA 1.5 g intravenously every 8 hours + metronidazole 500 mg intravenously every 8 hours

† 1 gram intravenously every 8 hours

‡ The 95% confidence interval (CI) was calculated as an unstratified Wilson Score CI.

Table 9: Clinical Cure Rates by Pathogen in a Phase 3 Trial of Complicated Intra-abdominal Infections (MITT Population)

Organism Group Pathogen	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Aerobic Gram-negative		
Escherichia coli	216/255 (84.7)	238/270 (88.1)
Klebsiella pneumoniae	31/41 (75.6)	27/35 (77.1)
Pseudomonas aeruginosa	30/38 (79)	30/34 (88.2)
Enterobacter cloacae	21/26 (80.8)	24/25 (96)
Klebsiella oxytoca	14/16 (87.5)	24/25 (96)
Proteus mirabilis	11/12 (91.7)	9/10 (90)
Aerobic Gram-positive		
Streptococcus anginosus	26/36 (72.2)	24/27 (88.9)
Streptococcus constellatus	18/24 (75)	20/25 (80)
Streptococcus salivarius	9/11 (81.8)	9/11 (81.8)
Anaerobic Gram-negative		
Bacteroides fragilis	42/47 (89.4)	59/64 (92.2)
Bacteroides ovatus	38/45 (84.4)	44/46 (95.7)
Bacteroides thetaiotaomicron	21/25 (84)	40/46 (87)
Bacteroides vulgatus	12/15 (80)	24/26 (92.3)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cIAI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 53/601 (9%). Cure rates in this subset were similar to the overall trial results. *In vitro* susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC ≤ 2 mcg/mL), while some others were not susceptible (MIC >2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

14.2 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 1068 adults hospitalized with cUTI (including pyelonephritis) were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) intravenously every 8 hours to levofloxacin (750 mg intravenously once daily) for 7 days of therapy. The primary efficacy endpoint was defined as complete resolution or marked improvement of the clinical symptoms and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) at the test-of-cure (TOC) visit 7 (± 2) days after the last dose of study drug. The primary efficacy analysis population was the microbiologically modified intent-to-treat (mMITT) population, which included all patients who received study medication and had at least 1 baseline uropathogen. The key secondary efficacy endpoint was the composite microbiological and clinical cure response at the TOC visit in the microbiologically evaluable (ME) population, which included protocol-adherent mMITT patients with a urine culture at the TOC visit.

The mMITT population consisted of 800 patients with cUTI, including 656 (82%) with pyelonephritis. The median age was 50.5 years and 74% were female. Concomitant bacteremia was identified in 62 (7.8%) patients at baseline; 608 (76%) patients were enrolled in Eastern Europe and 14 (1.8%) patients were enrolled in the United States.

ZERBAXA demonstrated efficacy with regard to the composite endpoint of microbiological and clinical cure at the TOC visit in both the mMITT and ME populations (Table 10). Composite microbiological and clinical cure rates at the TOC visit by pathogen in the mMITT population are presented in Table 11.

In the mMITT population, the composite cure rate in ZERBAXA-treated patients with concurrent bacteremia at baseline was 23/29 (79.3%).

Although a statistically significant difference was observed in the ZERBAXA arm compared to the levofloxacin arm with respect to the primary endpoint, it was likely attributable to the 212/800 (26.5%) patients with baseline organisms non-susceptible to levofloxacin. Among patients infected with a levofloxacin-susceptible organism at baseline, the response rates were similar (Table 10).

Table 10: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections

Analysis Population	ZERBAXA* n/N (%)	Levofloxacin† n/N (%)	Treatment Difference (95% CI)‡
mMITT	306/398 (76.9)	275/402 (68.4)	8.5 (2.3, 14.6)
Levofloxacin resistant baseline pathogen(s)	60/100 (60)	44/112 (39.3)	
No levofloxacin resistant baseline pathogen(s)	246/298 (82.6)	231/290 (79.7)	
ME	284/341 (83.3)	266/353 (75.4)	8.0 (2.0, 14.0)

* ZERBAXA 1.5 g intravenously every 8 hours
† 750 mg intravenously once daily
‡ The 95% confidence interval was based on the stratified Newcombe method.

Table 11: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections, in Subgroups Defined by Baseline Pathogen (mMITT Population)

Pathogen	ZERBAXA n/N (%)	Levofloxacin n/N (%)
Escherichia coli	247/305 (81)	228/324 (70.4)
Klebsiella pneumoniae	22/33 (66.7)	12/25 (48)
Proteus mirabilis	11/12 (91.7)	6/12 (50)
Pseudomonas aeruginosa	6/8 (75)	7/15 (46.7)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cUTI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 104/687 (15%). Cure rates in this subset were similar to the overall trial results. *In vitro* susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC ≤2 mcg/mL), while some others were not susceptible (MIC >2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

14.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

A total of 726 adult patients hospitalized with HABP/VABP were enrolled in a multinational, double-blind study (NCT02070757) comparing ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) intravenously every 8 hours to meropenem (1 g intravenously every 8 hours) for 8 to 14 days of therapy. All patients had to be intubated and on mechanical ventilation at randomization.

Efficacy was assessed based on all-cause mortality at Day 28 and clinical cure, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-

cure (TOC) visit which occurred 7 to 14 days after the end of treatment. The analysis population was the intent-to-treat (ITT) population, which included all randomized patients.

Following a diagnosis of HABP/VABP and prior to receipt of first dose of study drug, if required, patients could have received up to a maximum of 24 hours of active non-study antibacterial drug therapy in the 72 hours preceding the first dose of study drug. Patients who had failed prior antibacterial drug therapy for the current episode of HABP/VABP could be enrolled if the baseline lower respiratory tract (LRT) culture showed growth of a Gram-negative pathogen while the patient was on the antibacterial therapy and all other eligibility criteria were met. Empiric therapy at baseline with linezolid or other approved therapy for Gram-positive coverage was required in all patients pending baseline LRT culture results. Adjunctive Gram-negative therapy was optional and allowed for a maximum of 72 hours in centers with a prevalence of meropenem-resistant *P. aeruginosa* more than 15%.

Of the 726 patients in the ITT population the median age was 62 years and 44% of the population was 65 years of age and older, with 22% of the population 75 years of age and older. The majority of patients were white (83%), male (71%) and were from Eastern Europe (64%). The median APACHE II score was 17 and 33% of subjects had a baseline APACHE II score of greater than or equal to 20. All subjects were on mechanical ventilation and 519 (71%) had VABP. At randomization, 92% of subjects were in the ICU, 77% had been hospitalized for 5 days or longer, and 49% were ventilated for 5 days or longer. A total of 258 of 726 (36%) patients had CrCl less than 80 mL/min at baseline; among these, 99 (14%) had CrCl less than 50 mL/min. Patients with end-stage renal disease (CrCl less than 15 mL/min) were excluded from the trial. Approximately 13% of subjects were failing their current antibacterial drug therapy for HABP/VABP, and bacteremia was present at baseline in 15% of patients. Key comorbidities included diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease at rates of 22%, 16%, and 12%, respectively. In both treatment groups, most subjects (63.1%) received between 8 and 14 days of study therapy as specified in the protocol.

Table 12 presents the results for Day 28 all-cause mortality and clinical cure at the TOC visit overall and by ventilated HABP and VABP.

Table 12: Day 28 All-cause Mortality and Clinical Cure Rates at TOC from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (ITT Population)

Endpoint	ZERBAXA	Meropenem	Treatment Difference (95% CI)*
Day 28 All-cause Mortality	87/362 (24.0)	92/364 (25.3)	1.1 (-5.13, 7.39)
VABP	63/263 (24.0)	52/256 (20.3)	-3.6 (-10.74, 3.52)
Ventilated HABP	24/99 (24.2)	40/108 (37.0)	12.8 (0.18, 24.75)
Clinical Cure at TOC Visit	197/362 (54.4)	194/364 (53.3)	1.1 (-6.17, 8.29)
VABP	147/263 (55.9)	146/256 (57.0)	-1.1 (-9.59, 7.35)
Ventilated HABP	50/99 (50.5)	48/108 (44.4)	6.1 (-7.44, 19.27)

*The CI for overall treatment difference was based on the stratified Newcombe method with minimum risk weights. The CI for treatment difference of each primary diagnosis was based on the unstratified Newcombe method.

In the ITT population, Day 28 all-cause mortality and clinical cure rates in patients with CrCl greater than or equal to 150 mg/mL were similar between ZERBAXA and meropenem. In patients with bacteremia at baseline, Day 28 all-cause mortality rates were 23/64 (35.9%) for ZERBAXA-treated patients and 13/41 (31.7%) for meropenem-treated patients; clinical cure rates were 30/64 (46.9%) and 15/41 (36.6%), respectively.

Per pathogen Day 28 all-cause mortality and clinical cure at TOC were assessed in the microbiologic intention to treat population (mITT), which consisted of all randomized subjects who had a baseline lower respiratory tract (LRT) pathogen that was susceptible to both study treatments. In the mITT population, *Klebsiella pneumoniae* (113/425, 26.6%) and *Pseudomonas aeruginosa* (103/425, 24.2%) were the most prevalent pathogens isolated from baseline LRT cultures.

Day 28 all-cause mortality and clinical cure rates at TOC by pathogen in the mITT population are presented in Table 13. In the mITT population, clinical cure rates in patients with a Gram-negative

pathogen at baseline were 139/215 (64.7%) for ZERBAXA and 115/204 (56.4%) for meropenem, respectively.

Table 13: Day 28 All-cause Mortality and Clinical Cure Rates at TOC by Baseline Pathogen from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (mITT population)

Baseline Pathogen Category Baseline Pathogen	Day 28 All-cause Mortality		Clinical Cure at TOC	
	ZERBAXA n/N (%)	Meropenem n/N (%)	ZERBAXA n/N (%)	Meropenem n/N (%)
Pseudomonas aeruginosa	12/47 (25.5)	10/56 (17.9)	29/47 (61.7)	34/56 (60.7)
Enterobacteriaceae	27/161 (16.8)	42/157 (26.8)	103/161 (64.0)	87/157 (55.4)
Enterobacter cloacae	2/15 (13.3)	8/14 (57.1)	8/15 (53.3)	4/14 (28.6)
Escherichia coli	10/50 (20.0)	11/42 (26.2)	32/50 (64.0)	26/42 (61.9)
Klebsiella oxytoca	3/14 (21.4)	3/12 (25.0)	9/14 (64.3)	7/12 (58.3)
Klebsiella pneumoniae	7/51 (13.7)	13/62 (21.0)	34/51 (66.7)	39/62 (62.9)
Proteus mirabilis	5/22 (22.7)	5/18 (27.8)	13/22 (59.1)	11/18 (61.1)
Serratia marcescens	3/14 (21.4)	1/12 (8.3)	8/14 (57.1)	7/12 (58.3)
Haemophilus influenzae	0/20 (0)	2/15 (13.3)	17/20 (85.0)	8/15 (53.3)

In a subset of Enterobacteriaceae isolates from both arms of the trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 101/425 (23.8%). Day 28 all-cause mortality and clinical cure rates in this subset were similar to the overall trial results.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied in single-dose vials containing ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium) per vial. Vials are supplied in cartons containing 10 vials.

(NDC 67919-030-01)

16.2 Storage and Handling

ZERBAXA vials should be stored refrigerated at 2 to 8°C (36 to 46°F) and protected from light.

The reconstituted solution, once diluted, may be stored for 24 hours at room temperature or for 7 days under refrigeration at 2 to 8° C (36 to 46°F).

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patient that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask patient about any previous hypersensitivity reactions to ZERBAXA, other beta-lactams (including cephalosporins) or other allergens *[see Warnings and Precautions (5.2)]*.

Potentially Serious Diarrhea

Advise patient that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell patient to contact his or her healthcare provider *[see Warnings and Precautions (5.3)]*.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including ZERBAXA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZERBAXA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better

early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZERBAXA or other antibacterial drugs in the future *[see Warnings and Precautions (5.4)]*.

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MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: Steri-Pharma, LLC
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For patent information: www.merck.com/product/patent/home.html

uspi-mk7625a-iv-1906r004

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zerbaxa 1 g/0.5 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

After reconstitution with 10 mL diluent, the total volume of the solution in the vial is 11.4 mL, which contains 88 mg/mL of ceftolozane and 44 mg/mL of tazobactam.

Excipient with known effect
Each vial contains 10 mmol (230 mg) of sodium.

When the powder is reconstituted with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, the vial contains 11.5 mmol (265 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
(powder for concentrate).

White to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerbaxa is indicated for the treatment of the following infections in adults (see section 5.1):

- Complicated intra-abdominal infections (see section 4.4);
- Acute pyelonephritis;
- Complicated urinary tract infections (see section 4.4);
- Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The recommended intravenous dose regimen for patients with creatinine clearance > 50 mL/min is shown by infection type in Table 1.

Table 1: Intravenous dose of Zerbaxa by type of infection in patients with creatinine clearance > 50 mL/min

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated intra-abdominal infection*	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	4-14 days
Complicated urinary tract infection Acute pyelonephritis	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	7 days
Hospital-acquired pneumonia, including ventilator-associated pneumonia**	2 g ceftolozane / 1 g tazobactam	Every 8 hours	1 hour	8-14 days

*To be used in combination with metronidazole when anaerobic pathogens are suspected.
**To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

Special populations

Elderly (≥ 65 years of age)
No dose adjustment is necessary for the elderly based on age alone (see section 5.2).

Renal impairment
In patients with mild renal impairment (estimated creatinine clearance [CrCL] > 50 mL/min), no dose adjustment is necessary, see section 5.2.

In patients with moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table 2 (see sections 5.1 and 6.6).

Table 2: Recommended intravenous dose regimens for Zerbaxa in patients with creatinine clearance ≤ 50 mL/min

Estimated CrCL (mL/min)*	Complicated intra-abdominal infections, complicated urinary tract infections, and acute pyelonephritis**	Hospital-acquired pneumonia, including ventilator-associated pneumonia**
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours	1 g ceftolozane / 0.5 g tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
End stage renal disease on haemodialysis	A single loading dose of 500 mg ceftolozane / 250 mg tazobactam followed after 8 hours by a 100 mg ceftolozane / 50 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)	A single loading dose of 1.5 g ceftolozane / 0.75 g tazobactam followed after 8 hours by a 300 mg ceftolozane / 150 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)

*CrCL estimated using Cockcroft-Gault formula.
**All doses of Zerbaxa are administered intravenously over 1 hour and are recommended for all indications. The duration of treatment should follow the recommendations in Table 1.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Zerbaxa is for intravenous infusion.

The infusion time is 1 hour for all doses of Zerbaxa.

Precautions to be taken before handling or administering the product
See section 6.2 for incompatibilities.

See section 6.6 for instructions on reconstitution and dilution of the medicinal product before administration.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- Hypersensitivity to any cephalosporin antibacterial agent;
- Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible (see sections 4.3 and 4.8). If a severe allergic reaction occurs during treatment with ceftolozane/tazobactam, the medicinal product should be discontinued and appropriate measures taken.

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterial agents may also be hypersensitive to ceftolozane/tazobactam.

Ceftolozane/tazobactam is contraindicated in patients with a history of hypersensitivity to ceftolozane, tazobactam, or cephalosporins (see section 4.3).

Ceftolozane/tazobactam is also contraindicated in patients with severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems) (see section 4.3).

Ceftolozane/tazobactam should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or other beta-lactam antibacterial agents.

Effect on renal function

A decline in renal function has been seen in patients receiving ceftolozane/tazobactam.

Impaired renal function

The ceftolozane/tazobactam dose should be adjusted based on renal function (see section 4.2, Table 2).

In clinical trials of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis, the efficacy of ceftolozane/tazobactam was lower in patients with moderate renal impairment compared with those with normal or mildly impaired renal function at baseline. Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ceftolozane/tazobactam should be adjusted as necessary.

Limitations of the clinical data

Patients who were immunocompromised, patients with severe neutropenia, and patients with end stage renal disease on haemodialysis were excluded from clinical trials.

Complicated intra-abdominal infections
In a trial in patients with complicated intra-abdominal infections, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess (420/970 [43.3%] patients), of which 137/420 (32.6%) had diffuse peritonitis at baseline. Approximately 82% of all patients in the trial had APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of < 10 and 2.3% had bacteraemia at baseline. In the clinically evaluable (CE) patients, the clinical cure rates for ceftolozane/tazobactam were 95.9% in 293 patients aged less than 65 years and 87.8% in 82 patients aged 65 years or more.

Complicated urinary tract infections
Clinical efficacy data in patients with complicated lower urinary tract infection are limited. In a randomised active-controlled trial 18.2% (126/693) of microbiologically evaluable (ME) patients had complicated lower urinary tract infection, including 60/126 patients who were treated with ceftolozane/tazobactam. One of these 60 patients had bacteraemia at baseline.

Clostridioides difficile-associated diarrhoea

Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftolozane/tazobactam (see section 4.8). These types of infection may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftolozane/tazobactam. In such circumstances, the discontinuation of therapy with ceftolozane/tazobactam and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Non-susceptible micro-organisms

The use of ceftolozane/tazobactam may promote the overgrowth of non-susceptible micro-organisms. If super infection occurs during or following treatment, appropriate measures should be taken.

Ceftolozane/tazobactam is not active against bacteria that produce beta-lactamase enzymes which are not inhibited by tazobactam. See section 5.1.

Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with ceftolozane/tazobactam (see section 4.8). In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment.

Sodium content

Ceftolozane/tazobactam contains 230 mg sodium per vial, equivalent to 11.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 265 mg sodium per vial, equivalent to 13.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No significant medicinal product interactions are anticipated between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) based on *in vitro* and *in vivo* studies.

In vitro studies demonstrated that ceftolozane, tazobactam and the M1 metabolite of tazobactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations.

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K *in vitro* at therapeutic plasma concentrations. *In vitro* data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations.

Tazobactam is a substrate for OAT1 and OAT3. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. Co-administration of ceftolozane/tazobactam with OAT1 and OAT3 substrate furosemide in a clinical study did not significantly increase furosemide plasma exposures (geometric mean ratios of 0.83 and 0.87 for C_{max} and AUC, respectively). However, active substances that inhibit OAT1 or OAT3 (e.g., probenecid) may increase tazobactam plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ceftolozane/tazobactam in pregnant women. Tazobactam crosses the placenta. It is not known if ceftolozane crosses the placenta.

Animal studies with tazobactam have shown reproductive toxicity (see section 5.3) without evidence of teratogenic effects. Studies with ceftolozane in mice and rats have not shown evidence of reproductive toxicity or teratogenicity. Ceftolozane administered to rats during pregnancy and lactation was associated with a decrease in auditory startle response in postnatal day (PND) 60 male pups (see section 5.3).

Zerbaxa should only be used during pregnancy if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

It is unknown whether ceftolozane and tazobactam are excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zerbaxa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of ceftolozane and tazobactam on fertility in humans have not been studied. Fertility studies in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or intravenous administration of ceftolozane (see section 5.3).

4.7 Effects on ability to drive and use machines

Zerbaxa may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Zerbaxa (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Zerbaxa was evaluated in Phase 3 comparator-controlled clinical trials of complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis), which included a total of 1,015 patients, treated with Zerbaxa (1 g / 0.5 g intravenously every 8 hours, adjusted to match renal function where appropriate) for up to 14 days.

The most common adverse reactions (≥ 3% in pooled Phase 3 trials of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis) occurring in patients receiving Zerbaxa were nausea, headache, constipation, diarrhoea, and pyrexia and were generally mild or moderate in severity.

Zerbaxa was evaluated in a Phase 3 comparator-controlled clinical trial of hospital-acquired pneumonia, including ventilator-associated pneumonia, which included a total of 361 patients, treated with Zerbaxa (2 g / 1 g intravenously every 8 hours, adjusted to match renal function where appropriate) for up to 14 days.

The most common adverse reactions (≥ 5% in a Phase 3 trial of hospital-acquired pneumonia, including ventilator-associated pneumonia) occurring in patients receiving Zerbaxa were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased and were generally mild or moderate in severity.

Tabulated list of adverse reactions for complicated intra-abdominal infections, complicated urinary tract infections, including pyelonephritis, and hospital-acquired pneumonia, including ventilator-associated pneumonia

The following adverse reactions have been identified during clinical trials with Zerbaxa. Adverse reactions are classified according to MedDRA system organ class and frequency. Frequency categories are derived according to the following conventions: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) (see Table 3).

Table 3: Adverse reactions identified during clinical trials with ceftolozane/tazobactam

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Infections and infestations	*Clostridioides difficile* colitis[2]	Candidiasis including oropharyngeal and vulvovaginal[1], *Clostridioides difficile* colitis[1], fungal urinary tract infection[1], *Clostridioides difficile* infection[2]
Blood and the lymphatic system disorders	Thrombocytosis[1]	Anaemia[1]
Metabolism and nutrition disorders	Hypokalemia[1]	Hyperglycaemia[1], hypomagnesaemia[1], hypophosphataemia[1]
Psychiatric disorders	Insomnia[1], anxiety[1]	
Nervous system disorders	Headache[1], dizziness[1]	Ischemic stroke[1]
Cardiac disorders		Atrial fibrillation[1], tachycardia[1], angina pectoris[1]
Vascular disorders	Hypotension[1]	Phlebitis[1], venous thrombosis[1]
Respiratory, thoracic, and mediastinal disorders		Dyspnoea[1]
Gastrointestinal disorders	Nausea[1], diarrhoea[3], constipation[1], vomiting[3], abdominal pain[1]	Gastritis[1], abdominal distension[1], dyspepsia[1], flatulence[1], ileus paralytic[1]

System organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Skin and subcutaneous tissue disorders	Rash[1]	Urticaria[1]
Renal and urinary disorders		Renal impairment[1], renal failure[1]
General disorders and administration site conditions	Pyrexia[1], infusion site reactions[1]	
Investigations	Alanine aminotransferase increased[3], aspartate aminotransferase increased[3], transaminases increased[2], liver function test abnormal[2], blood alkaline phosphatase increased[2], gamma-glutamyltransferase increased[2]	Coombs test positive[3], increased serum gamma-glutamyl transpeptidase (GGT)[1], increased serum alkaline phosphatase[1], *Clostridioides* test positive[2]

[1] Specific for the complicated intra-abdominal infections, acute pyelonephritis, and complicated urinary tract infections indications treated with Zerbaxa (1 g / 0.5 g intravenously every 8 hours) for up to 14 days.
[2] Specific for the hospital-acquired pneumonia, including ventilator-associated pneumonia indication treated with Zerbaxa (2 g / 1 g intravenously every 8 hours) for up to 14 days.
[3] Applies across all indications: complicated intra-abdominal infections, acute pyelonephritis, complicated urinary tract infections, and hospital-acquired pneumonia, including ventilator-associated pneumonia.

Description of selected adverse reactions

Laboratory values
The development of a positive direct Coombs test may occur during treatment with Zerbaxa. The incidence of seroconversion to a positive direct Coombs test was 0.2% in patients receiving Zerbaxa and 0% in patients receiving the comparator in the complicated intra-abdominal infections and complicated urinary tract infections clinical trials. The incidence of seroconversion to a positive direct Coombs test was 31.2% in patients receiving Zerbaxa and 3.6% in patients receiving meropenem in the hospital-acquired pneumonia, including ventilator-associated pneumonia clinical trial. In clinical studies, there was no evidence of haemolysis in patients who developed a positive direct Coombs test in any treatment group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of Zerbaxa. The highest single dose of Zerbaxa used in clinical trials was 3 g / 1.5 g of ceftolozane/tazobactam administered to healthy volunteers.

In the event of overdose, Zerbaxa should be discontinued and general supportive treatment given. Zerbaxa can be removed by haemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the M1 metabolite of tazobactam were removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other cephalosporins and penems, ATC code: J01DI54.

Mechanism of action

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death.

Tazobactam is a beta-lactam structurally related to penicillins. It is an inhibitor of many molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes. See below.

Mechanisms of resistance

Mechanisms of bacterial resistance to ceftolozane/tazobactam include:

i. Production of beta-lactamases that can hydrolyse ceftolozane and which are not inhibited by tazobactam (see below)
ii. Modification of PBPs

Tazobactam does not inhibit all Class A enzymes.
In addition tazobactam does not inhibit the following types of beta-lactamase:

i. AmpC enzymes (produced by Enterobacterales)
ii. Serine-based carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemases [KPCs])
iii. Metallo-beta-lactamases (e.g., New Delhi metallo-beta-lactamase [NDM])
iv. Ambler Class D beta-lactamases (OXA-carbapenemases)

Pharmacokinetic/pharmacodynamic relationships

For ceftolozane the time that the plasma concentration exceeds the minimum inhibitory concentration of ceftolozane for the infecting organism has been shown to be the best predictor of efficacy in animal models of infection.

For tazobactam the PD index associated with efficacy was determined to be the percentage of the dose interval during which the plasma concentration of tazobactam exceeds a threshold value (%T > threshold). The time above a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in *in vitro* and *in vivo* non-clinical models.

Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

		Minimum Inhibitory Concentrations (mg/L)	
Pathogen	**Type of Infection**	**Susceptible**	**Resistant**
Enterobacterales	Complicated intra-abdominal infections* Complicated urinary tract infections* Acute pyelonephritis*	≤ 1	> 1
Enterobacterales	Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 2	> 2
P. aeruginosa	Complicated intra-abdominal infections* Complicated urinary tract infections* Acute pyelonephritis* Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 4	> 4
H. influenzae	Hospital-acquired pneumonia, including ventilator-associated pneumonia**	≤ 0.5	> 0.5

*Based on 1 g ceftolozane / 0.5 g tazobactam intravenously every 8 hours.
**Based on 2 g ceftolozane / 1 g tazobactam intravenously every 8 hours.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to Zerbaxa *in vitro*:

Complicated intra-abdominal infections

Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Gram-positive bacteria
Streptococcus anginosus
Streptococcus constellatus
Streptococcus salivarius

Complicated urinary tract infections, including pyelonephritis

Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

Hospital-acquired pneumonia, including ventilator-associated pneumonia

Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to Zerbaxa in the absence of acquired mechanisms of resistance:
Citrobacter freundii
Citrobacter koseri
Klebsiella (Enterobacter) aerogenes
Morganella morganii
Proteus vulgaris
Serratia liquefaciens

In vitro data indicate that the following species are not susceptible to ceftolozane/tazobactam:
Staphylococcus aureus
Enterococcus faecalis
Enterococcus faecium

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zerbaxa in one or more subsets of the paediatric population in complicated intra-abdominal infection, complicated urinary tract infection, and hospital-acquired pneumonia, including ventilator-associated pneumonia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The C_{max} and AUC of ceftolozane/tazobactam increase approximately in proportion to dose within ceftolozane single-dose range of 250 mg to 3 g and tazobactam single-dose range of 500 mg to 1.5 g. No appreciable accumulation of ceftolozane/tazobactam is observed following multiple 1-hour IV infusions of 1 g / 0.5 g ceftolozane/tazobactam or 2 g / 1 g ceftolozane/tazobactam administered every 8 hours for up to 10 days in healthy adults with normal renal function. The elimination half-life ($t_{½}$) of ceftolozane or tazobactam is independent of dose.

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is low (approximately 16% to 21% and 30%, respectively). The mean (coefficient of variation CV%) steady-state volume of distribution of ceftolozane/tazobactam in healthy adult males (n=51) following a single 1 g / 0.5 g IV dose was 13.5 L (21%) and 18.2 L (25%) for ceftolozane and tazobactam, respectively, similar to extracellular fluid volume.

Following 1 hour intravenous infusions of 2 g / 1 g ceftolozane/tazobactam or adjusted based on renal function every 8 hours in ventilated patients with confirmed or suspected pneumonia (N=22), ceftolozane and tazobactam concentrations in pulmonary epithelial lining fluid were greater than 8 mcg/mL and 1 mcg/mL, respectively, over 100% of the dosing interval. Mean pulmonary epithelial-to-free plasma AUC ratios of ceftolozane and tazobactam were approximately 50% and

62%, respectively and are similar to those in healthy subjects (approximately 61% and 63%, respectively) receiving 1 g / 0.5 g ceftolozane/tazobactam.

Biotransformation

Ceftolozane is eliminated in the urine as unchanged parent substance and thus does not appear to be metabolised to any appreciable extent. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive, tazobactam metabolite M1.

Elimination

Ceftolozane, tazobactam and the tazobactam metabolite M1 are eliminated by the kidneys. Following administration of a single 1 g / 0.5 g IV dose of ceftolozane/tazobactam to healthy male adults greater than 95% of ceftolozane was excreted in the urine as unchanged parent substance. More than 80% of tazobactam was excreted as the parent compound with the remaining amount excreted as the tazobactam M1 metabolite. After a single dose of ceftolozane/tazobactam, renal clearance of ceftolozane (3.41 - 6.69 L/h) was similar to plasma clearance (4.10 - 6.73 L/h) and similar to the glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is eliminated by the kidney via glomerular filtration.

The mean terminal elimination half-life of ceftolozane and tazobactam in healthy adults with normal renal function is approximately 3 hours and 1 hour, respectively.

Linearity/non-linearity

The C_{max} and AUC of ceftolozane/tazobactam increase in proportion to dose. Plasma levels of ceftolozane/tazobactam do not increase appreciably following multiple IV infusions of up to 2.0 g / 1.0 g administered every 8 hours for up to 10 days in healthy adults with normal renal function. The elimination half-life ($t_{½}$) of ceftolozane is independent of dose.

Special populations

Renal impairment

Ceftolozane/tazobactam and the tazobactam metabolite M1 are eliminated by the kidneys.

The ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects with normal renal function. The respective tazobactam dose normalized geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required (see section 4.2).

In subjects with end stage renal disease on haemodialysis, approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by haemodialysis. The recommended dose in complicated intra-abdominal infections, complicated urinary tract infections, and acute pyelonephritis subjects with end stage renal disease on haemodialysis is a single loading dose of 500 mg / 250 mg ceftolozane/tazobactam followed by a 100 mg / 50 mg maintenance dose of ceftolozane/tazobactam administered every 8 hours for the remainder of the treatment period. The recommended dose in hospital-acquired pneumonia, including ventilator-associated pneumonia subjects with end stage renal disease on haemodialysis is a single loading dose of 1.5 g / 0.75 g ceftolozane/tazobactam followed by a 300 mg / 150 mg maintenance dose of ceftolozane/tazobactam administered every 8 hours for the remainder of the treatment period. With haemodialysis, the dose should be administered immediately following completion of dialysis (see section 4.2).

Augmented renal clearance

Following a single 1-hour intravenous infusion of 2 g / 1 g ceftolozane/tazobactam to critically ill patients with CrCL greater than or equal to 180 mL/min (N=10), mean terminal half-life values of ceftolozane and tazobactam were 2.6 hours and 1.5 hours, respectively. Free plasma ceftolozane concentrations were greater than 8 mcg/mL over 70% of an 8-hour period; free tazobactam concentrations were greater than 1 mcg/mL over 60% of an 8-hour period. No dose adjustment of ceftolozane/tazobactam is recommended for hospital-acquired pneumonia, including ventilator-associated pneumonia patients with augmented renal clearance.

Hepatic impairment

As ceftolozane/tazobactam does not undergo hepatic metabolism, the systemic clearance of ceftolozane/tazobactam is not expected to be affected by hepatic impairment. No dose adjustment is recommended for ceftolozane/tazobactam in subjects with hepatic impairment (see section 4.2).

Elderly

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in exposure were observed with regard to age. No dose adjustment of ceftolozane/tazobactam based on age alone is recommended.

Paediatric patients

Safety and efficacy in paediatric patients have not been established.

Gender

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed for ceftolozane and tazobactam. No dose adjustment is recommended based on gender.

Ethnicity

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in ceftolozane/tazobactam AUC were observed in Caucasians compared to other ethnicities. No dose adjustment is recommended based on race.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies with ceftolozane/tazobactam have not been conducted.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: ceftolozane administered to rats during pregnancy and lactation was associated with a decrease in auditory startle response in postnatal day (PND) 60 male pups at maternal doses of 300 and 1,000 mg/kg/day. A dose of 300 mg/kg/day to rats was associated with a ceftolozane plasma exposure (AUC) value lower than the ceftolozane plasma AUC value at the highest recommended human dose of 2 grams every 8 hours.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam in the rat.

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that one of the active ingredients, ceftolozane, may pose a risk to surface water organisms (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Arginine
Citric acid, anhydrous

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 months.

After reconstitution, chemical and physical in-use stability has been demonstrated for 4 days at 2 to 8°C. The medicinal product is photosensitive and should be protected from light when not stored in the original carton.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Store in the original package in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL vial (Type I clear glass) with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

The powder for concentrate for solution for infusion for each vial is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following

reconstitution the vial should be shaken gently to dissolve the powder. The final volume is approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam) per vial.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

See section 4.2 for recommended dose regimens for Zerbaxa based on indication and renal function. The preparation for each dose is shown below.

For preparation of the 2 g ceftolozane / 1 g tazobactam dose: Withdraw the entire contents from two reconstituted vials (approximately 11.4 mL per vial) using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1.5 g ceftolozane / 0.75 g tazobactam dose: Withdraw the entire contents from one reconstituted vial (approximately 11.4 mL per vial) and 5.7 mL from a second reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1 g ceftolozane / 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 300 mg ceftolozane / 150 mg tazobactam dose: Withdraw 3.5 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment (see section 5.3). Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1032/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2015

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Laboratoires Merck Sharp & Dohme Chibret
Route de Marsat
Riom
63963, Clermont Ferrand Cedex 9
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zerbaxa 1 g / 0.5 g powder for concentrate for solution for infusion
ceftolozane / tazobactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam.

3. LIST OF EXCIPIENTS

Sodium chloride, arginine, citric acid, anhydrous

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1032/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Zerbaxa 1 g / 0.5 g powder for concentrate
ceftolozane / tazobactam

2. METHOD OF ADMINISTRATION

For IV use after reconstitution and dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zerbaxa 1 g / 0.5 g powder for concentrate for solution for infusion
ceftolozane / tazobactam

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerbaxa is and what it is used for

Zerbaxa is a medicine used to treat a range of bacterial infections. It contains two active substances:
- ceftolozane, an antibiotic that belongs to the group of "cephalosporins" and which can kill certain bacteria that can cause infection;
- tazobactam, which blocks the action of certain enzymes called beta-lactamases. These enzymes make bacteria resistant to ceftolozane by breaking down the antibiotic before it can act. By blocking their action, tazobactam makes ceftolozane more effective at killing bacteria.

Zerbaxa is used in adults to treat complicated infections within the abdomen, kidney and urinary system infections, and an infection of the lungs called "pneumonia".

2. What you need to know before you take Zerbaxa

Do not take Zerbaxa
- if you are allergic to ceftolozane, tazobactam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to medicines known as "cephalosporins".
- if you have had a severe allergic reaction (e.g., severe skin peeling; swelling of the face, hands, feet, lips, tongue or throat; or difficulty swallowing or breathing) to certain other antibiotics (e.g., penicillins or carbapenems).

Warnings and precautions
Talk to your doctor or pharmacist before taking Zerbaxa if you know you are, or have previously been allergic to cephalosporins, penicillins or other antibiotics.

Talk to your doctor or pharmacist if you develop diarrhoea while taking Zerbaxa.

Infections caused by bacteria that are not sensitive to Zerbaxa or caused by a fungus can occur during or following treatment with Zerbaxa. Tell your doctor if you think you may have another infection.

Treatment with Zerbaxa sometimes causes production of antibodies that react with your red blood cells. If you are told that you have an abnormal blood test (called Coombs test) tell your doctor that you are having or have recently had Zerbaxa.

Children and adolescents
This medicine should not be given to children under 18 years old because there is not enough information on use in this age group.

Other medicines and Zerbaxa
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Some medicines may interact with ceftolozane and tazobactam. These include:
- Probenecid (a medicine for gout). This can increase the time it takes for tazobactam to leave your body.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will advise if you should receive Zerbaxa during pregnancy.

If you are breast-feeding, your doctor will advise you on whether you should stop breast-feeding or stop or avoid Zerbaxa therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines
Zerbaxa may cause dizziness, which can affect your ability to drive and use machines.

Zerbaxa contains sodium
This medicine contains 230 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 11.5% of the recommended maximum daily dietary intake of sodium for an adult. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 265 mg sodium in each vial. This is equivalent to 13.3% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Zerbaxa

Your doctor or other healthcare professional will give you this medicine into one of your veins through an infusion (a drip) lasting one hour. The dose of medicine given to you depends on whether or not you have kidney problems.

<u>Adults</u>
The dose depends on the type of infection that you have, where the infection is in your body and how serious the infection is. Your doctor will decide on the dose that you need.

The recommended dose of Zerbaxa is 1 g of ceftolozane and 0.5 g of tazobactam or 2 g of ceftolozane and 1 g of tazobactam every 8 hours, which is given into one of your veins (directly into the bloodstream).

Treatment with Zerbaxa normally lasts between 4 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

Patients with kidney problems
Your doctor may need to reduce the dose of Zerbaxa or decide how often Zerbaxa is given to you. Your doctor may also want to test your blood to make sure you receive an appropriate dose, especially if you have to take this medicine for a long time.

If you take more Zerbaxa than you should
As this product is given by a doctor or other healthcare professional, it is very unlikely that you will be given too much Zerbaxa. However, if you have any concerns you should let your doctor, nurse or pharmacist know immediately.

If you stop taking Zerbaxa
If you think you have not been given a dose of Zerbaxa, tell your doctor or other healthcare professional immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you get these symptoms as you may need urgent medical treatment:
- Sudden swelling of your lips, face, throat or tongue; a severe rash; and, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening
- Diarrhoea that becomes severe or does not go away or stool that contains blood or mucus during or after treatment with Zerbaxa. In this situation, you should not take medicines that stop or slow bowel movement

Patients treated for complicated infections within the abdomen, and kidney and urinary system
Common side effects (may affect up to 1 in 10 people):
Headache, stomach ache, constipation, diarrhoea, nausea, vomiting, increase in liver enzymes (from blood tests), rash, fever (high temperature), decrease in blood pressure, decrease in potassium (from blood tests), increase in the number of certain types of blood cells known as platelets, dizziness, anxiety, difficulty sleeping, infusion site reactions

Uncommon side effects (may affect up to 1 in 100 people):
Inflammation of the large intestine due to *C. difficile* bacteria, inflammation of the stomach, abdominal distension, indigestion, excessive gas in stomach or bowel, obstruction of the intestine, yeast infection in the mouth (thrush), yeast infection of female genitalia, fungal urinary tract infection, increase in sugar (glucose) levels (from blood tests), decrease in magnesium levels (from blood tests), decrease in phosphate levels (from blood tests), ischemic stroke (stroke caused by reduced blood flow in brain), irritation or inflammation of a vein at injection site, venous thrombosis (blood clot in a vein), low red blood cell counts, atrial fibrillation (rapid or irregular heartbeat), fast heart beat, angina pectoris (chest pain or feeling of tightness, pressure or heaviness in chest), itchy rash or swellings on the skin, hives, Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells), kidney problems, kidney disease, shortness of breath

Patients treated for an infection of the lungs called “pneumonia”
Common side effects (may affect up to 1 in 10 people):
Inflammation of the large intestine due to *C. difficile* bacteria, diarrhoea, vomiting, increase in liver enzymes (from blood tests)

Uncommon side effects (may affect up to 1 in 100 people):
Infection due to *C. difficile* bacteria, *C. difficile* test positive (from stool test), Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerbaxa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after "EXP." The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2°C – 8°C).

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerbaxa contains
- The active substances are ceftolozane and tazobactam.
- Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam. For doses above 1 g ceftolozane and 0.5 g tazobactam, two vials are used.
- The other excipients are sodium chloride, arginine, and citric acid, anhydrous.

What Zerbaxa looks like and contents of the pack
Zerbaxa is a white to slightly yellow powder for concentrate for solution for infusion (powder for concentrate) supplied in a vial.

Zerbaxa is available in packs containing 20 mL Type I clear glass vial with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

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Laboratoires Merck Sharp & Dohme Chibret
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Preparation of solutions

Each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

The powder for concentrate for solution for infusion for each vial is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following reconstitution the vial should be shaken gently to dissolve the powder. The final volume is approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam) per vial.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

See section 4.2 of the Summary of Product Characteristics for recommended dose regimens for Zerbaxa based on indication and renal function. The preparation for each dose is shown below.

For preparation of the 2 g ceftolozane / 1 g tazobactam dose: Withdraw the entire contents from two reconstituted vials (approximately 11.4 mL per vial) using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1.5 g ceftolozane / 0.75 g tazobactam dose: Withdraw the entire contents from one reconstituted vial (approximately 11.4 mL per vial) and 5.7 mL from a second reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1 g ceftolozane / 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 300 mg ceftolozane / 150 mg tazobactam dose: Withdraw 3.5 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

After reconstitution, chemical and physical in-use stability has been demonstrated for 4 days at 2 to 8°C. The medicinal product is photosensitive and should be protected from light when not stored in the original carton.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions and would normally not be longer than 24 hours at 2 to 8°C.

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment. Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.