β-lactamase-encoding genes. The pursuit of adjuvants that inhibit β-lactamases is therefore crucial to retain clinical effectiveness of the β-lactam class of antibiotics. The recent approval of ceftolozane–tazobactam in 2014, ceftazidime–avibactam in 2015, and meropenem–vaborbactam by FDA in 2017 for the treatment of drug-resistant Gram-positive and GNB infections is indicative of the continued interest in the development of adjuvant combination therapies that includes a β-lactam and a β-lactamase inhibitor. At least four more β-lactam-based antibiotic–adjuvant combinations are currently in clinical trials (Taneja and Kaur 2016; Butler et al. 2017). We will briefly highlight a few recent examples.

## 18.7 Imipenem–Cilastatin/Relebactam Triple Combination

In 1985, the combination of the carbapenem, imipenem, and the adjuvant cilastatin was approved for use in the United States under the trade name Primaxin® (Jacobs 1986). Imipenem is a broad-spectrum antibiotic that is rapidly degraded by the human renal enzyme dehydropeptidase-1, and the resulting metabolite poses potential for nephrotoxicity (Hikida et al. 1992). Thus, addition of the dehydropeptidase-1 inhibitor cilastatin to imipenem prevents imipenem's degradation and nephrotoxicity. Cilastatin also blocks megalin-mediated proximal tubule uptake of cationic antibiotics (Hori et al. 2017), further lowering the risk of kidney damage. However, the recent increase in bacterial infections caused by carbapenemase-producing organisms that inactivate imipenem calls for an improvement in this therapy. The combination of imipenem–cilastatin with the addition of the diazabicyclooctane β-lactamase inhibitor relebactam is currently in phase III clinical trial for the treatment of GNB infections (Falagas et al. 2016). The adjuvant relebactam is able to inhibit the activity of ESBL, class A (e.g. KPC) and class C (e.g. AmpC) β-lactamases, against imipenem by irreversibly blocking their functional/reactive site (Blizzard et al. 2014). The triple combination was found to be generally well tolerated in patients, with commonly reported adverse effects being nausea, vomiting, and diarrhea (Lucasti et al. 2016). Recently, a phase III randomized, double-blind, non-inferiority study of imipenem-cilastatin/relebactam in comparison to imipenem–cilastatin/colistimethate sodium for the treatment of hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infection (cIAI), and complicated urinary tract infection (cUTI) (https://clinicaltrials.gov/ct2/show/study/NCT02452047) was completed. Results are yet to be disclosed. Another phase III randomized, double-blind, non-inferiority study of imipenem–cilastatin/relebactam against piperacillin-tazobactam for the treatment of HABP or VABP is currently recruiting (https://clinicaltrials.gov/ct2/show/