Imipenem + cilastatin + relebactam

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

EMLc | Codes ATC: J01DH56

Indication	Carbapenem-resistant Pseudomonas aeruginosa — Code ICD11: MG50.80
INN	Imipenem + cilastatin + relebactam
Type de médicament	Chemical agent
Groupes d'antibiotiques	R RESERVE
Type de liste	Liste complémentaire (EML) (EMLc)
Formulations	Parenteral > General injections > IV: 500 mg + 500 mg + 250 mg powder for injection
Historique des statuts LME	Demande refusée en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Imipenem + cilastatin + relebactam
DrugBank	Imipenem Cilastatin Relebactam

Recommandation du comité d'experts

The Expert Committee recognized the global health importance of effective new treatments for infections caused by multidrug-resistant pathogens, especially those designated as critical priority on the WHO priority pathogens list, for which few effective treatment options exist or are in development. The Committee noted that imipenem + cilastatin + relebactam has broad in vitro activity against multidrug-resistant Gram-negative pathogens but lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally. The Committee also noted that other Reserve antibiotic options which have a similar spectrum of activity are already included on the EML for the treatment of other types of carbapenem-resistance in Enterobacterales (e.g. cefiderocol, ceftazidime + avibactam and meropenem + vaborbactam). The Committee considered that the available clinical trial evidence for efficacy of imipenem + cilastatin + relebactam was generally positive, albeit limited, and noted that no serious safety or tolerability concerns were identified. The Committee also noted the high price of the medicine compared with older antibiotics, but also that it has been found to be acceptably cost-effective at willingness-to-pay thresholds in high-income settings. Based on these considerations, the Expert Committee did not recommend the inclusion of imipenem + cilastatin + relebactam as a Reserve group antibiotic for the treatment of infections caused by multidrug-resistant organisms on the EML.

Contexte

Imipenem + cilastatin + relebactam has not previously been considered for inclusion on the EML. It has been classified as a reserve group antibiotic under the AWaRe (Access–Watch–Reserve) classification.

Pertinence pour la santé publique

Worldwide in 2019, an estimated 4.95 million people died of drug-resistant bacterial infections, of which 1.27 million were directly attributable to resistant infections, most of these were concentrated in low- and middle-income countries. Drug-resistant Pseudomonas aeruginosa was responsible for 84 600 deaths, of which almost half were carbapenem-resistant, drug-resistant Klebsiella pneumoniae was responsible for 193 000 deaths, of which almost 30% were carbapenem-resistant and drug-resistant Escherichia coli was responsible for 219 000 deaths, of which almost 15% were carbapenem-resistant (1). Antibiotic resistance among Gram-negative pathogens is a problem worldwide. The European Centre for Disease Prevention and Control reported increasing trends of carbapenem resistance in invasive isolates of K. pneumoniae (+ 20% in 2021 compared with the previous year) with a population-weighted mean of 11.7%, (range 0–73.7%) in 2021 (2). Population-weighted mean resistance percentages among K. pneumoniae invasive isolates were also very high for other antibiotic classes, in particular for third-generation cephalosporins (34.3%), fluoroquinolones (33.6%) and aminoglycosides (23.7%) with about a third of K. pneumoniae cases (34.3%) in the European Union/European Economic Area resistant to at least one antimicrobial class under surveillance in 2021. For P. aeruginosa, no increasing trend of carbapenem-resistance in the 2017–2021 period was reported, even though levels remain high in some countries, with a mean of 18.1% among invasive isolates in the European Union/European Economic Area in 2021 and wide intercountry variation (3.5% to 45.9%). Additionally, 18.7% of isolates were resistant to at least one antimicrobial classes under surveillance. In the United States, the proportions of carbapenem-resistant K. pneumoniae and P. aeruginosa isolates have decreased overall since 2011 among tracked health care-associated infections. In 2020, the mean national resistance level was 4.8% for Klebsiella and 12.9% for Pseudomonas (compared to 9.8% and 20.0%, respectively in 2011); however, wide variation exist across states (3). In 2017, WHO designated carbapenem-resistant P. aeruginosa and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales critical priority pathogens in need of new therapeutic options (4).

Bénéfices

Randomized clinical trials RESTORE-IMI 1 was a randomized, double-blind, multicentre, phase III trial that investigated the activity of imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) compared with colistin (300 mg loading dose, then 150 mg every 12 hours) plus imipenem + cilastatin relebactam (500 mg + 500 mg every 6 hours) for the treatment of complicated intra-abdominal and urinary tract infections and hospital acquired pneumonia, including ventilator-associated pneumonia (5). The primary efficacy endpoint was overall response, however the study was not powered to infer statistically significant differences in efficacy between treatment arms. The trial only included patients with infections caused by imipenem non-susceptible (but colistin susceptible) Gram-negative pathogens in adults and excluded patients with Acinetobacter spp. infections. There were 31 and 16 patients in the intervention group and comparator group, respectively. The primary outcome was calculated on the microbiological modified intention-to-treat population which included 21 and 10 patients in the intervention and comparator groups, respectively. These were patients with a positive culture for an imipenem-resistant Gram-negative pathogen that had received at least one dose of the study medicine. Most patients had Pseudomonas infections – 80% in the comparator group and 76% in the intervention group. Overall, the β-lactamases most frequently detected were AMPc (84%) and extended-spectrum β-lactamases (35%). Carbapenemases were detected in a minority of patient with Klebsiella pneumoniae carbapenemase detected in five patients (of whom four were randomized to imipenem + cilastatin + relebactam) and OXA-48 in one patient randomized to the control group. Despite being protocol-required, only nine patients had baseline blood cultures and only two of those had a bacteraemia. A favourable overall response was reported in 71.4% and 70.0% of patients in the intervention and comparator groups, respectively. The overall adjusted difference for favourable response was −7.3% (90% confidence interval (CI) −27.7% to 21.4%), favouring the comparator group. Definitions of overall response differed by type of infection: for hospital-acquired pneumonia/ventilator-associated pneumonia, it was survival at day 28; for complicated intra-abdominal infections it was clinical response at day 28; and for complicated urinary tract infections it was clinical plus microbiological response 5–9 days after the end of therapy. A favourable clinical response at day 28 was reported in 71.4% and 40.0% of patients in the intervention and comparator groups, respectively (adjusted difference 26.3%, 90% CI 1.3% to 51.5%). Among secondary endpoints, all-cause

mortality at day 28 was lower in the intervention group (9.5% versus 30%; adjusted difference −17.3%, 90% CI −46.4% to 6.4%). Results by type of infection showed that for hospital-acquired pneumonia/ventilator-associated pneumonia 28-day survival was 20.8% higher with imipenem + cilastatin + relebactam (87.5% versus 66.7%). None of the four patients with a complicated intra-abdominal infections had a favourable response at day 28 while for complicated urinary tract infections, results for the primary efficacy endpoint favoured the comparator group with an adjusted difference of −27.3% (90% CI −52.8% to 12.8%). Of the two patients with bacteraemia (randomized one to each group) only the one in the comparator group had a favourable response. The RESTORE-IMI 2 was a randomized controlled, double-blind, multicentre, non-inferiority, phase III trial comparing imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) with piperacillin + tazobactam (4 g + 500 mg every 6 hours) for the treatment of hospital-acquired pneumonia/ventilator-associated pneumonia in adults (6). Treatment duration was 7–14 days. In total, 537 patients were included, 268 in the intervention group and 269 in the comparator group. The primary and secondary outcomes were evaluated in the modified intention-to-treat population, which excluded patients where only Gram-positive cocci were isolated at baseline. Results for the primary endpoint of 28-day all-cause mortality showed lower mortality in the intervention group (15.9% versus 21.3%) with an adjusted difference of −5.3% (95% CI −11.9% to 1.2%). With a prespecified 10% margin, non-inferiority was concluded. The key secondary endpoint was favourable clinical response at early follow-up (7–14 days after the end of treatment). Results favoured the intervention group (61.0% versus 55.8%) with an adjusted difference of 5.0% (95% CI −3.2% to 13.2%). With a prespecified 12.5% margin, non-inferiority was concluded. At day 28, a favourable clinical response was reported in 51.9% of patients in the intervention group and 50.6% in the comparator group, with an adjusted difference of 1.1% (95% CI −7.2% to 9.4%). The application also presented findings from a series of post-hoc and secondary analyses of the RESTORE-IMI 2 trial presented at conferences that reported results for imipenem + cilastatin + relebactam in patients with imipenem-resistant infections, in critically ill patients, in patients with renal augmentation or impairment, and in patients with polymicrobial hospital-acquired pneumonia/ventilator-associated pneumonia infections (7–10). A randomized, double-blind, multicentre, non-inferiority, dose-ranging, phase II study compared the efficacy of relebactam 250 mg, relebactam 125 mg or placebo each given with imipenem + cilastatin for the treatment of 351 adult patients with complicated intra-abdominal infections regardless of baseline susceptibility of the pathogen (11). The primary efficacy endpoint was favourable clinical response at discontinuation of therapy (5–9 days after the start of therapy) and at late follow-up (28–42 days). With a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint. A similar study was conducted in adult patients with complicated urinary tract infections regardless of baseline susceptibility of the pathogen (12). Again, with a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint of the proportion of patients who achieved a favourable microbiological response. Observational studies A retrospective case series described outcomes in 21 adult patients with mixed infection sources (52% were pulmonary infections) who were treated with imipenem + cilastatin + relebactam. Most infections were caused by P. aeruginosa (16/21, 76%), of which all except one were multidrug-resistant. Survival at 30 days was observed in 67% of patients. Two patients experienced adverse events, neither of which led to treatment discontinuation. Imipenem + cilastatin + relebactam was used as combination therapy in 29% of cases (6/21), with tobramycin as the most common concomitant antibiotic (13).

Torts

The applicants presented the safety data for imipenem + cilastatin + relebactam for each interventional study in the previous section. In the RESTORE-IMI 1 trial, adverse events were recorded during therapy and in the 14-day follow-up period. Overall, the incidence of adverse events, deaths, serious adverse events, drug-related adverse events and discontinuations due to adverse events was lower with imipenem + cilastatin + relebactam than with colistin plus imipenem + cilastatin; however, the trial was not powered to detect statistical significance in safety outcomes. Drug-related adverse events were reported in 16.1% (5/31) of patients treated with imipenem + cilastatin + relebactam and in 31.3% (5/16) of patients in the comparator group. Two patients discontinued treatment in the comparator group because of a drug-related adverse event and none discontinued in the imipenem + cilastatin + relebactam group. No serious drug-related adverse events were reported in either group. Treatment-emergent nephrotoxicity was significantly lower with imipenem + cilastatin + relebactam than with colistin plus imipenem + cilastatin: 3/29 (10.3%) versus 9/16 (56.3%), P = 0.002 (5). In the RESTORE-IMI 2 trial, adverse events were recorded during therapy and in the 14-day follow-up period. The incidence of adverse events, deaths, serious adverse events, drug-related adverse events and discontinuations due to adverse events were comparable between patients who received imipenem + cilastatin + relebactam and those who received piperacillin + tazobactam. Drug-related adverse events were reported in 11.7% of patients treated with

imipenem + cilastatin + relebactam and in 9.7% of patients in the comparator group. In total 10 patients had to discontinue therapy due to a drug-related adverse event – 6/266, 2.3% in the imipenem + cilastatin + relebactam and 4/269, 1.5% in the comparator group. Five serious drug-related adverse event were reported, three in the imipenem + cilastatin + relebactam (of whom two had to discontinue therapy) and two with piperacillin + tazobactam (with therapy discontinued in one) (6). In the dose-ranging study in patients with complicated intra-abdominal infections, drug-related adverse events occurred in 13.7% (16/117) of patients treated with imipenem + cilastatin + relebactam 250 mg, 13.8% (16/116) of patients treated with imipenem + cilastatin + relebactam 125 mg and in 9.6% (11/114) of patients treated with imipenem cilastatin monotherapy. In total, four patients discontinued therapy due to a drug-related adverse event, three in the monotherapy group and one in the imipenem + cilastatin + relebactam 125 mg group. One patient in the monotherapy group had a serious drug-related adverse event necessitating discontinuation of therapy (11). In the dose-ranging study in patients with complicated urinary tract infections, drug-related adverse events occurred in 10.1% (10/99) of patients treated with imipenem + cilastatin + relebactam 250 mg, 9.1% (9/99) of patients treated with imipenem + cilastatin + relebactam 125 mg and in 9.0% (9/100) of patients treated with imipenem + cilastatin monotherapy. Four patients discontinued therapy due to a drug-related adverse event, of whom one was in the monotherapy group. Two serious drug-related adverse events were reported, one in the imipenem + cilastatin + relebactam 250 mg and one in the monotherapy group (12).

Rapport coût/efficacité

The application presented the findings of a cost–effectiveness analysis of imipenem + cilastatin + relebactam compared with colistin plus imipenem + cilastatin using clinical data from the RESTORE-IMI 1 trial. On average, a patient treated with imipenem + cilastatin + relebactam gained additional 3.7 quality adjusted life years (QALYs) over their lifetime. Higher drug acquisition costs for imipenem + cilastatin + relebactam were offset by shorter length of hospital stay and lower costs related to adverse events, which resulted in net savings of US$ 11 015 per patient. Sensitivity analyses suggested that imipenem + cilastatin + relebactam had a high likelihood of being cost-effective at a US willingness-to-pay threshold of US$ 100 000–150 000 per QALY (15). A second cost–effectiveness analysis compared imipenem + cilastatin + relebactam and piperacillin + tazobactam using clinical data from the RESTORE-IMI 2 trial. QALYs gained were reported as 7.92 and 7.08 for imipenem + cilastatin + relebactam and piperacillin + tazobactam, respectively. Total treatment costs were US$ 185 254 and US$ 170 513 for imipenem + cilastatin + relebactam and piperacillin + tazobactam, respectively. This resulted in an incremental cost per QALY gained of US$ 17 529, which is lower than the typical US willingness-to-pay threshold. The authors concluded that imipenem + cilastatin + relebactam may be a cost-effective treatment for payers and a valuable option for clinicians (16).

Directives de l'OMS

Imipenem + cilastatin + relebactam is not currently included in WHO guidelines. WHO recognized its usefulness against carbapenem-resistant Enterobacterales but noted the uncertainty on its activity against P. aeruginosa due to inconclusive data (14).

Disponibilité

Imipenem + cilastatin + relebactam is manufactured by Merck and has regulatory approval from the United States Food and Drug Administration and the European Medicines Agency. It is currently available in 19 European countries, in the United States and in Japan. Market availability is currently pending in Argentina, Belgium, Denmark, Ireland, Palau and Spain.

Autres considérations

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML as a reserve group antibiotic. The technical department stressed that the use of imipenem + cilastatin + relebactam must be always informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries. The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML as a reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms, but emphasized the importance of associated stewardship interventions to ensure its appropriate use. The Working Group highlighted that imipenem + cilastatin + relebactam has broad activity against extended-spectrum β-lactamase-producing Enterobacterales, some carbapenemase-producing Enterobacterales (mainly Class A Klebsiella

pneumoniae carbapenemase and Class C AmpC, but not Class B metallo-β-lactamases and Class D OXA) and carbapenem-resistant P. aeruginosa. Although New Delhi metallo-β-lactamases and Class D OXA carbapenemases are globally the most common genotypes associated with carbapenem resistance in Enterobacterales, Klebsiella pneumoniae carbapenemase remains an important cause in some low- and middle-income countries, where treatment options are limited. Infections caused by carbapenem-resistant Enterobacterales and carbapenem-resistant P. aeruginosa are a major public health concern and in many low- and middle-income countries settings, antibiotic treatment options are now very limited; indeed, the only options may be older agents with important toxicity concerns, such as colistin. The Working Group noted that some clinical trial and observational data suggest that imipenem + cilastatin + relebactam had clinical efficacy in patients with infections caused by multidrug-resistant pathogens. Although the medicine has limited activity against some types of carbapenem resistance, it has good activity against other types seen in both high-income countries and low- and middle-income countries. The Working Group also noted that the medicine is well tolerated, with no specific safety concerns. However, imipenem + cilastatin + relebactam is significantly more expensive than antibiotics for which generics are available and there are few cost–effectiveness data in low- and middle-income settings.

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