TRANSPARENCY COMMITTEE SUMMARY 23 SEPTEMBER 2020

The legally binding text is the original French opinion version

imipenem/cilastatin/relebactam
RECARBRIO 500 mg/500 mg/250 mg powder for solution for infusion

First assessment

► Key points

Positive opinion for reimbursement in the market authorisation (MA) indications, only as a last resort for patients' treatment with enterobacteria infections, sensitive to the imipenem/cilastatin/relebactam combination, and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem-cilastatin) cannot be considered in case of resistance, in particular through KPC-type carbapenemase production.

Negative opinion for reimbursement in other situations.

► What therapeutic improvement?

Therapeutic improvement in patient care management.

► Role in the care pathway?

In June 2019, the HAS published guidelines relating to antibiotics management therapy of Enterobacteriaceae and *Pseudomonas aeruginosa* infections in adults, specifying the role of carbapenems and their alternatives.

Role of the medicinal product in the care pathway

RECARBRIO (imipenem/cilastatin/relebactam) is a last resort treatment, in the same way as VABOREM (meropenem/vaborbactam), restricted for patients with enterobacteria infections sensitive to the imipenem/cilastatin/relebactam combination and for whom recourse to carbapenems cannot be considered in case of resistance, in particular with a KPC type resistance mechanism.

RECARBRIO (imipenem/cilastatin/relebactam) should not be used as an alternative to carbapenems for the treatment of TGC-resistant enterobacteria and for the treatment of *P. aeruginosa* infections.

It should not be used as probabilistic treatment but solely on the basis of microbiological documentation.

► Special recommendations

Given the product characteristics and the need to restrict its use to a last resort treatment only to preserve it, the therapeutic decision should be taken alongside antibiotic experts, with systematic reassessment 48 hours after treatment initiation.

COMMITTEE'S CONCLUSIONS

Clinical benefit

- ▶ The infections concerned by this proprietary medicinal product are life-threatening for patient's prognosis, either directly or as a result of complications.
- ▶ It is a curative treatment.
- ▶ The efficacy/adverse effects ratio is high.
- ▶ There are few therapeutic alternatives.
- ▶ It is a last-resort treatment.

Public health impact

Considering:

- the frequency and seriousness of the infections concerned,
- the medical need to have access to new antibiotics in order to respond to the spread of antibiotics' resistance, of those currently used.
- the response to the identified need, due to its possible use in particular therapeutic pathway, as infections caused by carbapenem-resistant and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE),
- the expected impact on morbidity and mortality in patients with enterobacteria infections sensitive to imipenem/cilastatin/relebactam and for whom recourse to carbapenems cannot be considered in case of resistance, in particular through KPC-type carbapenemase production,
- the expected impact on the care and life pathway of patients.

RECARBRIO (imipenem/cilastatin/relebactam) is likely to have, in the same way as VABOREM (meropenem/vaborbactam), an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RECARBRIO (imipenem/cilastatin/relebactam) is:

- **substantial only as a last resort for patients' treatment with enterobacteria infections sensitive to the imipenem/cilastatin/relebactam combination and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem/cilastatin) cannot be considered in case of resistance, in particular through KPC-type carbapenemase production;**
- **insufficient to justify public funding cover in all other clinical situations.**

The Committee issues a positive opinion for RECARBRIO's inclusion (imipenem/cilastatin/relebactam) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indications and dosages, only as a last resort for patients' treatment with enterobacteria infections sensitive to the imipenem/cilastatin/relebactam combination and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem/cilastatin) cannot be considered in case of resistance, in particular through KPC-type carbapenemase production.

The Committee issues a negative opinion for RECARBRIO's inclusion (imipenem/cilastatin/relebactam) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in other situations.

Clinical Added Value

Considering:

- its *in vitro* activity on class A Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae (ESBL-PE), particularly KPC type;
- experience acquired with imipenem/cilastatin, a carbapenem widely used in the treatment of severe nosocomial infections due to Gram-negative bacteria;
- the demonstrated efficacy of the imipenem/cilastatin/relebactam combination in mild to moderate hospital-acquired pneumonia, with a satisfactory safety profile;
- limited clinical data (RESTORE-IMI-1 study) suggesting high efficacy in patients with carbapenem-resistant enterobacteria infections (CRE), primarily through KPC-type carbapenemase production;
- the fact that the imipenem/cilastatin/relebactam combination is one of the few current antibiotics active on certain carbapenemase-producing enterobacteria;

the Committee considers that RECARBRIO (imipenem/cilastatin/relebactam), in the same way as VABOREM (meropenem/vaborbactam), provides a moderate clinical added value (CAV III) in the treatment of enterobacteria infections sensitive to the imipenem/cilastatin/relebactam combination and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem-cilastatin) cannot be considered in case of resistance.