BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ZAVICEFTA, (ceftazidime/avibactam), cephalosporin and β-lactamase inhibitor

Minor improvement in the treatment of infections caused by extended-spectrum beta-lactamase-producing enterobacteriaceae or by *P. aeruginosa* as an alternative to treatment with carbapenem

Main points

- **ZAVICEFTA** has Marketing Authorisation in the treatment of complicated intra-abdominal infections, complicated urinary tract infections including acute pyelonephritis, hospital-acquired pneumonia including ventilator-associated pneumonia, infections due to aerobic Gram-negative bacteria in adults for whom therapeutic options are limited.

- Its potential benefit lies in its action against certain resistant Gram-negative bacteria, making it possible to treat patients with suspected or documented enterobacter infections due to extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae or to *Pseudomonas aeruginosa*, within the framework of a carbapenem-sparing regimen. It may be offered in infections due to Gram-negative bacteria, as an alternative to the use of carbapenems, in case of documented or highly suspected resistance to third-generation cephalosporins, and when use of the ceftazidime/avibactam combination is appropriate.

- There is insufficient documentation of its clinical efficacy in severe infections and/or infections caused by multidrug-resistant bacteria.

Therapeutic use

- **Complicated intra-abdominal infections**
  The probabilistic treatment for complicated intra-abdominal infections, in the absence of any risk factor for multiresistant bacteria, is the fixed-dose combination of piperacillin +/- amikacin (for 2 to 3 days) over a period of 10 +/- 4 days.
  In the event of a risk of appearance of multidrug-resistant bacteria, treatment relies on carbapenem +/- amikacin (for 2 to 3 days) for a period of 15 +/- 8 days.
  The alternatives in the case of allergy to beta-lactams are:
  - ciprofloxacin + amikacin + metronidazole + vancomycin;
  - aztreonam + amikacin + metronidazole + vancomycin;
  or, if there are no alternatives: ciprofloxacin + tigecycline.

  In light of the clinical data, the natural resistance of the enterococci and of anaerobic bacteria (including Bacteroides and Clostridium) in this type of infection and in a hospital-acquired context, ZAVICEFTA, in combination with metronidazole, may be offered in complicated intra-abdominal infections due to documented susceptible ESBL-producing enterobacteriaceae or *Pseudomonas aeruginosa*.

- **Complicated urinary infections and acute pyelonephritis**
  In the absence of any risk of ESBL-producing enterobacteriaceae, ceftriaxone or cefotaxime are part of the first-line probabilistic treatments. In the event of a risk of ESBL-producing enterobacteriaceae, the probabilistic treatment is based on the combination of carbapenem + aminoside, or in case of allergy, aztreonam + aminoside.
  In case of documented infection with these enterobacteriaceae, fluoroquinolones are preferably recommended (levofloxacine); sulfamethoxazole-trimethoprim or the piperacillin-tazobactam combination can also be offered if the strain is susceptible to it.

  Given the clinical data, ZAVICEFTA can be offered in complicated urinary tract infections (including pyelonephritis) due to susceptible ESBL-producing enterobacteriaceae or *Pseudomonas aeruginosa*.
- **Hospital-acquired pneumonia**

In the event of diagnosis of hospital-acquired pneumonia, antibiotic therapy should be started probabilistically, without waiting for the microbiological results (with certain exceptions). The choice of probabilistic antibiotic therapy depends essentially on the time to onset (early or late pneumonia), the existence of risk factors for multidrug-resistant pathogens and the existence of previous antibiotic therapy.

The preliminary results of a study, the pharmacokinetic characteristics of ZAVICEFTA and clinical experience with ceftazidime alone, suggest that it may be offered in the treatment of hospital-acquired pneumonia due to susceptible ESBL-producing enterobacteraeae or *Pseudomonas aeruginosa*. These considerations should be confirmed by the definitive results of a clinical study.

- **Infections due to Gram-negative aerobic bacteria in adult patients for whom therapeutic options are limited**

It is recommended that ZAVICEFTA be used for treatment of infections due to Gram-negative aerobic bacteria in adults for whom therapeutic options are limited, only in accordance with the advice of a doctor experienced in the management of infectious diseases.

**Clinical data**

- The efficacy of the ceftazidime/avibactam combination (2 g/0.5 g every 8 hours by intravenous infusion over 2 hours) has been demonstrated only in the treatment of urinary tract infections (including pyelonephritis) and intra-abdominal infections, of low to moderate severity, including strains resistant to third-generation cephalosporins.

- Its use to treat patients with hospital-acquired pneumonia, including ventilator-associated pneumonia, and to treat patients with infections due to Gram-negative bacteria for whom therapeutic options are limited, is based on experience with ceftazidime alone and on analysis of the pharmacokinetic-pharmacodynamic relationship of ceftazidime/avibactam.

- Clinical efficacy has not been established against the following Gram-negative bacteria, which are relevant in consideration of the approved indications, although *in vitro* studies suggest that these bacteria might be susceptible to ceftazidime/avibactam in the absence of acquired resistance mechanisms: *Citrobacter koseri, Enterobacter aerogenes, Morganella morganii, Proteus vulgaris, Providencia rettgeri*, *Serratia marcescens*. Moreover, *in vitro* the following species are not susceptible to ceftazidime/avibactam: *Staphylococcus aureus* (methicillin susceptible and resistant), *Anaerobic bacteria, Enterococcus spp, Stenotrophomonas maltophilia* and *Acinetobacter spp*.

- The safety was comparable to that of beta-lactams. The most common adverse effects (≥ 3% in grouped phase III trials) occurring in patients receiving ZAVICEFTA (± metronidazole) were nausea, diarrhoea, headache, vomiting and fever, and were mild or moderate in severity. A positive direct Coombs test was also frequently reported.

**Special prescribing conditions**

- Medicine for hospital prescription

**Benefit of the medicinal product**

- The actual benefit* of ZAVICEFTA is substantial
- ZAVICEFTA provides minor clinical added value** (CAV IV) in the treatment.
- Recommends inclusion on the list of reimbursable products for hospital use.

This document was created on the basis of the Transparency Committee Opinion of 30 November 2016 (CT-15531) and is available at www.has-sante.fr

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

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