SUMMARY

rezafungin

REZZAYO 200 mg

powder for concentrate for solution for infusion

First listing

Adopted by the Transparency Committee on 29 May 2024

Summary of opinion

Favourable opinion for reimbursement only for the treatment of invasive candidiasis in non-neutropenic adults.

Unfavourable opinion for reimbursement in the other situations covered by the MA indication.

Transparency Committee's conclusions

Clinical Benefit

- Invasive *Candida spp.* fungal infections can be life-threatening in the immediate term or following complications. Neutropenia is a risk factor and a major severity factor.
- This is a curative medicinal product.
- The efficacy/adverse effects ratio is high in the treatment of invasive candidiasis in non-neutropenic adults. It is inadequately established in neutropenic adults. The data reported in the context of the ReSTORE pivotal study are limited (8/100 in the rezafungin group and 5/99 in the caspofungin group having an ANC < 500 cells/µL) not permitting assessment of the clinical benefit of rezafungin (REZZAYO) in this population. The Committee considers that the level of evidence of the data remains lower than that for the other three echinocandins, caspofungin, anidulafungin and micafungin and regrets the absence of a comparative study versus another echinocandin or liposomal amphotericin B. On the basis of currently available data, the Committee deems that REZZAYO (rezafungin) has no role in the treatment of invasive candidiasis in neutropenic patients.
- The therapeutic alternatives are the echinocandins, caspofungin and micafungin and the other antifungals indicated in the curative treatment of invasive candidiasis.

➔ Public health benefit

Considering:

- the seriousness of invasive candidiasis, with an estimated incidence of candidaemia in France of 2.5 per 100,000 people between 2001 and 2010, having increased by around 8% in the past ten years;
- the partially met medical need in adult patients with severe invasive candidiasis, particularly in the event of concomitant neutropenia;
- the partial response to the identified need given:
  - the absence of a demonstrated additional impact on morbidity and mortality in terms of global response at D14 (EMA endpoint) and all-cause mortality at D30 (FDA endpoint) compared to caspofungin (ReSTORE non-inferiority study, with no demonstration or superiority),
  - the limited level of evidence in the neutropenic patient population due to a low number of inclusions in the ReSTORE study;
- the lack of evidence of an impact on quality of life and the organisation of care,
- an expected, but not demonstrated, impact on the care and/or life pathway, particularly in patients with a difficult venous approach and requiring prolonged treatment (half-life of 80 hours after the first dose and 150 hours after the second or third dose).

REZZAYO (rezafungin) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of REZZAYO (rezafungin) is:

- **substantial only in the treatment of invasive candidiasis in non-neutropenic adults;**
- **insufficient to justify public funding cover in view of the available alternatives in the other MA situations (neutropenic adults).**

The Committee issues the following opinions:

- **a favourable opinion for inclusion of REZZAYO (rezafungin) in the list of covered drugs for inpatients approved for use in the treatment of invasive candidiasis in non-neutropenic adults, and at the MA dosages.**
- **an unfavourable opinion for inclusion of REZZAYO (rezafungin) in the list of covered drugs for inpatients approved for use in the other situations covered by the MA (neutropenic adults).**

Clinical Added Value

Considering:

- the partially met medical need in adult patients with severe invasive candidiasis, particularly in the event of concomitant neutropenia;
- the demonstrated non-inferiority of rezafungin compared to caspofungin in terms of (ITTm analysis):
  - global response at D14 (EMA endpoint): 59.1% (55/93) versus 60.6% (57/94), i.e. an adjusted difference = -1.1%, $CI_{95\%}$ [-14.9; 12.7],
  - all-cause mortality at D30 (FDA endpoint): 23.7% (22/93) versus 21.3% (20/94), i.e. an adjusted difference of 2.4%, $CI_{95\%}$ [-9.7; 14.4];

- an acceptable safety profile but marked by adverse events, such as injection-related reactions, tremor and phototoxicities;

but:

- a very wide non-inferiority bound in terms of global response and mortality compared to caspofungin, accepting a loss of efficacy risk of up to 20% compared to the comparator (non-inferiority threshold scheduled in the protocol);
- the absence of a reduction in mortality rate compared to caspofungin (superiority still to be demonstrated);
- a limited transposability of the results in the population of interest with a more severe prognosis, in particular:
  - the non-inclusion of severe hepatic impairment or with a complex infection (endocarditis, osteoarticular infection, endophthalmitis, central nervous system infections, chronic disseminated candidiasis, urinary infection),
  - a confirmed diagnosis of invasive candidiasis in only a third of patients,
  - a low number of neutropenic patients (absolute neutrophil count < 500 cells/µL): 8/100 in the rezafungin group and 5/99 in the caspofungin group,
  - an APACHE score ≥ 20 in approximately 17% of patients;
- the absence of data on treatment failures and/or resistances of the strains selected in the clinical trials;

the Committee considers that REZZAYO (rezafungin) provides no clinical added value (CAV V) in the treatment of invasive candidiasis in non-neutropenic adults.