HAUTE AUTORITÉ DE SANTÉ

ASSESSING HEALTH TECHNOLOGIES

OPINION ON MEDICINAL PRODUCTS

enfortumab vedotin
PADCEV 20 mg and 30 mg,

powder for solution for dilution for infusion

First assessment

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, who have previously received chemotherapy based on platinum salts and a programmed death receptor-1 inhibitor (anti-PD-1) or a programmed death receptor ligand-1 inhibitor (anti-PD-L1).

Therapeutic improvement?

Therapeutic improvement in the therapeutic strategy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, who have previously received chemotherapy based on platinum salts and an anti-PD-1 drug or an anti-PD-L1 drug.

Role in therapeutic strategy?

As a first-line approach, treatment is based on polychemotherapy based on platinum salts. For patients eligible for cisplatin (creatinine clearance > 60 ml/min, ECOG 0 or 1), the GC (gemcitabine, cisplatin), MVAC-HD (methotrexate, vinblastine, adriamycin and cisplatin), MVAC or PCG (paclitaxel, cisplatin, gemcitabine) regimens may be used.

For patients ineligible for cisplatin, chemotherapy based on carboplatin is recommended (particularly carboplatin + gemcitabine). For patients ineligible for cisplatin with PD-L1 marker + tumour expression, atezolizumab (anti-PD-L1) and pembrolizumab (anti-PD1) have been granted a marketing authorisation, but are not covered for this indication in France.

Note that, for patients whose disease has not progressed after platinum-based chemotherapy, the use of BAVENCIO (avelumab) as monotherapy is indicated as maintenance treatment. Regarding patients experiencing progression after platinum salt-based chemotherapy, immunotherapy treatments (pembrolizumab, atezolizumab and nivolumab) have been granted a marketing authorisation in Europe. The French CCAFU 2020-2022 guidelines recommend using pembrolizumab (KEYTRUDA), the only immunotherapy treatment covered in France.

According to ESMO, after relapse from platinum salt-based chemotherapy treatment and immunotherapy treatment (anti-PD1 or anti-PD-L1), the available alternatives are enfortumab vedotin, taxane-based chemotherapy regimens (docetaxel, paclitaxel), vinflunine.

Role of the medicinal product

PADCEV (enfortumab vedotin), as monotherapy is a third-line treatment after a chemotherapy regimen based on platinum salts and an anti-PD-1 or anti-PD-L1 drug in patients with locally advanced or metastatic urothelial carcinoma.

PADCEV (enfortumab vedotin), as monotherapy is a second-line treatment after maintenance treatment with BAVENCIO (avelumab).

The Committee points out that in accordance with the SPC, “patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤ 1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see Section 4.2 of the SPC).”

Considering the skin toxicity, the Committee recommends setting up oncologist and dermatologist collaboration to define the most suitable treatment (including in particular discontinuing PADCEV (enfortumab vedotin)) from the onset of an initial sign of skin toxicity.

Special recommendations

Considering the uncertainty around the safety of PADCEV (enfortumab vedotin), the Committee shall reassess this proprietary medicinal product within not less than two years from the date of this opinion. The Committee requests to be a recipient of reports analysing the pharmacovigilance data in respect of this proprietary medicinal product.

Committee's conclusions

Clinical Benefit

- Urothelial carcinoma is a serious life-threatening disease.
- The proprietary medicinal product PADCEV (enfortumab vedotin) is a curative medicinal product.
- Its efficacy/adverse effect ratio is significant, considering:
  - evidence of superiority versus chemotherapy particularly in overall survival with however,
  - increased toxicity with the onset of grade ≥ 3 adverse events in 72.6% versus 67.4% in the chemotherapy group, particularly the onset of skin toxicity, hyperglycaemia and peripheral sensory neuropathy and
  - reported cases of severe skin toxicity, sometimes of fatal outcome, observed in compassionate use.
- Alternative medications are available for patients who have previously received chemotherapy based on platinum salts and an anti-PD-1 or anti-PD-L1 drug.
- This therapy is a third-line treatment after a chemotherapy regimen based on platinum salts and an anti-PD-1 or anti-PD-L1 drug in patients with locally advanced or metastatic urothelial carcinoma. PADCEV (enfortumab vedotin) is a second-line treatment after maintenance treatment with BAVENCIO (avelumab).

Public health benefit

Considering:

- the severity and prevalence of urothelial carcinoma,
- the insufficiently met medical need,
- the partial response to the identified need and particularly the evidence of the additional impact on mortality in the pivotal study. However, concerns remain primarily around skin toxicities with a fatal outcome observed in certain cases in compassionate use,
- the lack of evidence of an additional impact on quality of life,
- the lack of data making it possible to assess the additional impact on delivery of care, but accounting for the dosage requiring intravenous infusion of enfortumab vedotin on days 1, 8 and 15 of a 28-day cycle,

PADCEV (enfortumab vedotin) is not likely to have an additional public health benefit.

Considering all of these elements, the Committee deems that the actual clinical benefit of PADCEV (enfortumab vedotin) is significant in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and at the marketing authorisation dosages.

Clinical Added Value

Considering:

- the evidence of the superiority of PADCEV (enfortumab vedotin) versus chemotherapy (taxanes or vinflunine), in an open-label, randomised phase III study, in terms of overall survival, with a point estimation of absolute gain of 3.91 months, (HR = 0.702 [95%CI: 0.556 - 0.886], and in progression-free survival (modest difference of +1.84 months),
- the medical need currently insufficiently met by the alternatives available

and despite:

- increased toxicity with the onset of grade ≥ 3 adverse events in 72.6% of patients versus 67.4% in the chemotherapy group, particularly the onset of more frequent skin toxicity, hyperglycaemia and peripheral sensory neuropathy than the chemotherapy group,
- reported cases of severe skin toxicity, sometimes of fatal outcome, observed in compassionate use,
- a lack of evidence of improvement of quality of life,

the Transparency Committee deems that PADCEV (enfortumab vedotin) provides minor clinical added value (CAV IV) in the therapeutic strategy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have previously received chemotherapy based on platinum salts and an anti-PD-1 or anti-PD-L1 drug.