OPINION ON MEDICINAL PRODUCTS

elotuzumab
EMPLICITI 300 mg and 400 mg,
powder for solution for dilution for infusion
New indication

Adopted by the Transparency Committee on 18 January 2023

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement in association with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least two previous treatments, including lenalidomide and a proteasome inhibitor, and whose disease progressed during the most recent treatment.

Therapeutic improvement?

No therapeutic improvement with respect to the pomalidomide and dexamethasone association.

Role in therapeutic strategy?

For symptomatic patients, the first treatment is dependent on whether the patient is eligible for intensive chemotherapy associated with autologous peripheral blood stem cell transplantation (APBSCT). DARZALEX (daratumumab) has also been included in the therapeutic strategy as a first treatment, regardless of APBSCT status, in association with regimens including an immunomodulatory drug IMID (thalidomide or REVLIMID (lenalidomide)) and/or a proteasome inhibitor PI [VELCADE (bortezomib)] and/or melphalan.

In the event of relapse or progression after the first treatment, the therapeutic decision is dependent on age, previous treatments, duration of the first remission, and the circumstances of the relapse, PBC availability, the patient's general state of health and comorbidities. The treatments are based on a bitherapy or tritherapy associating pomalidomide (IMNOVID), daratumumab (DARZALEX), ixazomib (NINLARO) or carfilzomib (KYPROLIS), isatuximab (SARCLISA) with bortezomib (VELCADE) or with lenalidomide (REVLIMID) and/or with dexamethasone.

From the second relapse, for patients previously treated with VELCADE (bortezomib) and REVLIMID (lenalidomide), IMNOVID (pomalidomide) has been granted a marketing authorisation in association with dexamethasone. Nevertheless due to updates to the therapeutic strategy for multiple myeloma with new medicinal products joining the therapeutic arsenal at an earlier stage, the role of IMNOVID (pomalidomide) in association with dexamethasone has become restricted. Furthermore, the earlier use of IMNOVID (pomalidomide) in the context of an association with bortezomib and dexamethasone should considerably reduce the benefit of pomalidomide/dexamethasone bitherapy in subsequent treatments. FARYDAK (panobinostat) in association with bortezomib and dexamethasone is another therapeutic option as a last-resort treatment, for relapsed and/or refractory myeloma having already received two previous two lines of treatment including bortezomib and an IMID. DARZALEX (daratumumab) is also an option for relapsed and refractory multiple myeloma patients, whose previous treatments included a PI and an IMID; nevertheless, its earlier use (currently possible as first treatment) in the context of an association with a PI or with an IMID, considerably reduces the benefit of this monotherapy in subsequent treatments. SARCLISA (isatuximab) has been included in the therapeutic strategy in association with pomalidomide and with dexamethasone for patients having received at least two previous treatments including lenalidomide and a PI.

Beyond that, for heavily pre-treated patients at a very advanced phase, BLENREP (belantamab mafodotin) has been granted a marketing authorisation for the treatment of adult multiple myeloma patients, having received at least 4 previous treatments and whose disease is refractory to at least an proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody, and whose disease progressed during the most recent treatment. The Transparency Committee deemed it to be a secondary treatment, when all treatment options have been exhausted, following a multidisciplinary review meeting opinion.

ABECMA (idecabtagene vicleucel) was also granted a marketing authorisation for relapsed and refractory multiple myeloma patients, who have received at least three previous treatments, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment. The Transparency Committee deemed that it was fourth-line or subsequent treatment, and that it was not possible to specify its role in relation to BLENREP (belantamab mafodotin) on account of the lack of methodologically robust comparative data.

Recently, CARVYKTI (ciltacabtagene autoleucel) was granted a marketing authorisation for the treatment of relapsed and refractory adult multiple myeloma patients, having received at least three

previous treatments. TECVAYLI (teclistamab) has been granted a conditional marketing authorisation for this indication.

Role of EMPLICITI (elotuzumab) in the therapeutic strategy:

The association of EMPLICITI (elotuzumab) with pomalidomide and dexamethasone is a treatment of multiple myeloma (MM), in adult relapsed and refractory patients, who have received at least two previous treatments, including lenalidomide and a proteasome inhibitor, and whose disease progressed during the most recent treatment.

Nevertheless, the Committee would like to point out the late filing of the reimbursement application for EMPLICITI (elotuzumab) and the update of the treatment strategy of multiple myeloma at prior lines of treatment. Consequently, the transposability of the findings of the ELOQUENT-3 study to the current strategy is not guaranteed and the role of EMPLICITI (elotuzumab) is difficult to determine. The Committee also points out the lack of availability of data on the efficacy of the E-Pd association after DARZALEX (daratumumab) treatment, which is recommended from the first line of treatment, regardless of autologous peripheral blood stem cell transplantation eligibility status.

Finally, the role of the E-Pd regimen, versus currently recommended regimens from the third line of treatment, and CAR-T therapies indicated from the fourth line of treatment is not known.

Committee's conclusions

Actual Clinical Benefit

- Multiple myeloma is a blood disorder of almost always fatal outcome with a short median survival (3 to 5 years).
- The proprietary medicinal product EMPLICITI (elotuzumab) is a specific curative multiple myeloma medicinal product.
- The efficacy/adverse effect ratio is low considering the low level of evidence of the phase II study (with a high alpha risk of 20%) and the toxicity profile.
- Therapeutic alternatives are available (see Section 5. Clinically relevant comparators).

  The association of EMPLICIT (elotuzumab) with pomalidomide and dexamethasone is a treatment of multiple myeloma (MM), in adult relapsed and refractory patients, who have received at least two previous treatments, including lenalidomide and a proteasome inhibitor, and whose disease progressed during the most recent treatment. Nevertheless, the Committee would like to point out the late filing of the reimbursement application for EMPLICITI (elotuzumab) and the rapid update of the treatment strategy of multiple myeloma at prior lines of treatment. Consequently, the transposability of the findings of the ELOQUENT-3 study to the current strategy is not guaranteed and the role of EMPLICITI (elotuzumab) is difficult to determine. The Committee also points out the lack of availability of data on the efficacy of the E-Pd association after DARZALEX (daratumumab) treatment, which is recommended from the first line of treatment, regardless of autologous peripheral blood stem cell transplantation eligibility status. Finally, the role of the E-Pd regimen, versus currently recommended regimens from the third line of treatment, in particular CAR-T therapies indicated from the fourth line of treatment is not known.

Public health benefit

Considering:

- the severity of multiple myeloma and its incidence,
- the medical need partially met by the medicinal products available,
- the lack of response to the identified need on account of:
  - the lack of evidence of an additional impact of the EMPLICITI (elotuzumab) + pomalidomide + dexamethasone (E-Pd) association on morbidity-mortality versus the pomalidomide + dexamethasone (Pd) association (phase II study with a high α risk of 20%, introduction of ranking not initially planned),
  - the lack of robust data on quality of life supporting an improvement of quality of life among treated patients,
- the lack of evidence of an impact on delivery of care,

EMPLICITI (elotuzumab) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of EMPLICITI (elotuzumab) is low 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 dosages.

Clinical Added Value

Considering:

- the data from the phase II study, ELOQUENT-3, suggesting a difference of +5.6 months in median progression-free survival of the EMPLICITI (elotuzumab) association with pomalidomide and dexamethasone versus the pomalidomide and dexamethasone association, a clinically relevant comparator on the date of completion of the study,

but considering on the other hand:

- the low level of evidence of these data from a phase II study with a high alpha risk of 20%, which resembles a proof of concept and which must be confirmed by a phase III study,
- the transposability of the findings of this study to current clinical practice which cannot be guaranteed, considering the late filing of the reimbursement application (marketing authorisation of 2019) and the update of the therapeutic strategy with the arrival of new medicinal products, as well as the use of DARZALEX (daratumumab) in earlier lines of treatment. Furthermore, the pomalidomide and dexamethasone association, considered as a relevant comparator at the time of the ELOQUENT-3 study, is no longer considered as a third-line treatment of choice,
- the safety profile marked by the onset of severe infections (41.7% versus 27.3%),
- the lack of robust data on quality of life,

the Transparency Committee deems that EMPLICITI (elotuzumab) in association with pomalidomide and dexamethasone provides no clinical added value (CAV V) with respect to the pomalidomide and dexamethasone association.

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