SUMMARY

exagamglogene autotemcel

CASGEVY 4 to 13 x 10^6 cells/mL

dispersion for perfusion

First listing

Adopted by the Transparency Committee on 28 August 2024

Summary of opinion

Favourable opinion for reimbursement only in "the treatment of severe sickle cell disease (SCD) in patients 12 to 35 years of age with recurrent vaso-occlusive crises (VOCs) despite well managed hydroxycarbamide treatment for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available and the severity of the disease has been established by:

- **the implementation of a transfusion programme for at least 6 months for recurrent vaso-occlusive episodes (paediatric and adult population),**
- **AND/OR, for the adult population only, the persistence of vaso-occlusive episodes having required conventional hospitalisation in the past year (≥ 2 episodes/year or ≥ 1 episode/year having required transfusion)**

The Committee makes maintenance of the moderate clinical benefit conditional on reevaluation of the medicinal product within a maximum period of 3 years, based on the additional results requested.

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

Transparency Committee's conclusions

Clinical Benefit

- Sickle cell disease is a condition with a very variable course. It is associated with the development of haemolytic anaemia, the acute and chronic complications of which significantly impair the quality of life of patients and can ultimately be life-threatening. In patients with sickle cell disease, deaths are primarily related to cerebral, renal, cardiac, pulmonary and hepatic complications. Life expectancy is lower than in the population as a whole and is estimated to be around 50 years according to recent data.
- This is intended as a curative medicinal product, although this has not yet been demonstrated.

- ➔ The efficacy/adverse effects ratio is still to be established in view of the conditional MA due to the still limited data available (interim analyses on a small number of patients with a short follow-up duration in a non-comparative study) and the current uncertainties that these data raise (with respect to the potential curative nature, the mobilisation difficulties and the efficacy and safety in the longer term), but which suggest a short-term efficacy on the prevention of VOCs, with 96.6% of evaluable patients having received CASGEVY (exagamglogene autotemcel) not having presented a severe VOC for 12 consecutive months.
- ➔ In the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available, on the basis of currently available data and the uncertainties these raise, CASGEVY (exagamglogene autotemcel):
  - is a salvage therapy **to be reserved only** for patients 12 to 35 years of age with recurrent vaso-occlusive crises (VOCs) despite well managed hydroxycarbamide treatment and for whom the severity of the disease has been established by:
    - the implementation of a transfusion programme for at least 6 months for recurrent vaso-occlusive episodes (paediatric and adult population),
    - AND/OR, for the adult population only, the persistence of vaso-occlusive episodes having required conventional hospitalisation in the past year (≥ 2 episodes/year or ≥ 1 episode/year having required transfusion).
  - Has no role in the care pathway in other clinical situations.
- ➔ **Public health benefit**

Considering:

- the seriousness of the disease, which can be life-threatening, and the low prevalence of severe sickle cell disease,
- the partially met medical need,
- the partial response to the identified need given:
  - an expected additional impact on morbidity (the occurrence of VOCs) in the most severe patients having already received the optimal therapy in France, although this has currently not been demonstrated in view of the preliminary data available and the uncertainties that these raise,
  - but the lack of evidence of an impact on mortality and quality of life;
  - the lack of evidence of an additional impact on the organisation of care,

CASGEVY (exagamglogene autotemcel) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CASGEVY 4 to 13 x 10^6 cells/mL (exagamglogene autotemcel) is:

- **moderate in the treatment of severe sickle cell disease (SCD) only in patients 12 to 35 years of age with recurrent vaso-occlusive crises (VOCs) despite well managed hydroxycarbamide treatment for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available and the severity of the disease has been established by:**
  - **the implementation of a transfusion programme for at least 6 months for recurrent vaso-occlusive episodes (paediatric and adult population),**

- **AND/OR, for the adult population only, the persistence of vaso-occlusive episodes having required conventional hospitalisation in the past year (≥ 2 episodes/year or ≥ 1 episode/year having required transfusion),**

– **insufficient to justify public funding in the other MA situations.**

The Committee issues the following opinions:

– **a favourable opinion for inclusion of CASGEVY 4 to 13 x 10^6 cells/mL (exagamglogene autotemcel) in the list of covered drugs for inpatients approved for use in the treatment of severe sickle cell disease (SCD) only in patients 12 to 35 years of age with recurrent vaso-occlusive crises (VOCs) despite well managed hydroxycarbamide treatment for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available and the severity of the disease has been established by:**

- **the implementation of a transfusion programme for at least 6 months for recurrent vaso-occlusive episodes (paediatric and adult population),**
- **AND/OR, for the adult population only, the persistence of vaso-occlusive episodes having required conventional hospitalisation in the past year (≥ 2 episodes/year or ≥ 1 episode/year having required transfusion),**

– **an unfavourable opinion for inclusion of CASGEVY 4 to 13 x 10^6 cells/mL (exagamglogene autotemcel) in the list of covered drugs for inpatients approved for use in the other situations covered by the MA.**

The Committee makes maintenance of the moderate clinical benefit conditional on reevaluation of the medicinal product within a maximum period of 3 years, based on the additional results requested.

Clinical Added Value

➔ Within the reimbursement scope

Considering:

– The available data, from the CLIMB-121 non-comparative pivotal study and the CLIMB-131 follow-up study, in favour of the efficacy of exagamglogene autotemcel on the short-term prevention of VOCs, with 96.6% of the patients having received the treatment not having presented any severe vaso-occlusive crises for 12 consecutive months over a 16-month follow-up period (primary endpoint of the CLIMB-121 study), clinically relevant endpoints for the disease,

But also considering:

– The population on which the efficacy endpoint is measured, which raises questions since it excludes patients who were mobilised but discontinued the study before the administration of CASGEVY (exagamglogene autotemcel). In fact, the CASGEVY treatment strategy starts from the time of mobilisation. Hence, also considering patients having discontinued the study before receiving CASGEVY (exagamglogene autotemcel) (n=46) in the analysis, or those having discontinued the study before having received CASGEVY (exagamglogene autotemcel) but having started the mobilisation phase (n=40), the response rates for the

primary endpoint were, respectively, 60.9% (CI95%: 45.4% - 74.9%, n=28/46) and 70.0% (CI95%: 53.5% - 83.4%, n=28/40),

- The lack of comparative data enabling the value of this gene therapy to be assessed in comparison with current management,
- The preliminary nature of these data, produced from interim analyses on a small number of patients (n=29) followed up for a short period of time, raising the question of a possible over-estimation of the effects presented and uncertainties with respect to the curative nature of this gene therapy, the mobilisation difficulties and its efficacy and safety in the longer term (particularly the theoretical tumour risk),
- The potential heterogeneity of the patients in the study in terms of disease severity, which cannot be assessed due to a lack of sufficient data collected to document it,

the Committee deems that CASGEVY 4 to 13 x 10^6 cells/mL (exagamglogene autotemcel) provides no clinical added value (CAV V) in the current care pathway, which includes the relevant comparators.