SUMMARY

exagamglogene autotemcel

CASGEVY 4 to 13 x 10^6 cells/mL

dispersion for infusion

First listing

Adopted by the Transparency Committee on 25 September 2024

Summary of opinion

Favourable opinion for reimbursement only in patients 12 to 35 years of age in the indication "treatment of transfusion-dependent β-thalassaemia (TDT) in patients for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available"

The Committee makes maintenance of the substantial 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 (patients over 35 years of age).

Transparency Committee's conclusions

Clinical Benefit

- β-thalassaemia is a serious disease responsible for severe, early-onset anaemia in the event of major forms in which current standard therapy is based on a life-long transfusion programme. The main complications of the disease are associated with post-transfusion iron overload, with cardiac damage in the long term (congestive heart failure, arrhythmia or sudden death) and significant morbidity due to iron deposits in the liver and glands. It causes severe fatigability as a result of anaemia, significantly impairing patients' quality of life.
- This is a curative medicinal product, although its long-term efficacy has not yet been fully demonstrated.
- The efficacy/adverse effects ratio is:
  - **high in patients 12 to 35 years of age**,
  - **not established in patients over 35 years of age** in the absence of evaluation in this population.

➔ It is an alternative to the standard symptomatic treatment of transfusion-dependent β-thalassaemia (TDT), i.e. blood transfusions combined with iron chelation therapy administered for life, only in transfusion-dependent patients 12 to 35 years of age for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available.

➔ Public health benefit

Considering:

- the seriousness of the disease, which can be life-threatening, and the low prevalence of transfusion-dependent β-thalassaemia,
- the medical need partially met by blood transfusions combined with iron chelation therapy,
- the partial response to the identified need given:
  - an expected additional impact on patient morbidity in terms of transfusion dependence, with, according to short-term data from an interim analysis in the pivotal study, 92.9% (n=39/42) of evaluable patients having achieved transfusion independence for 12 consecutive months (86.7% (n=39/45) when all the patients mobilised are taken into account),
  - uncertainties concerning the curative nature (persistence of ineffective erythropoiesis for half of patients) and maintenance of long-term efficacy,
  - but the lack of evidence of an impact on mortality and quality of life;
- the impact of CASGEVY (exagamglogene autotemcel) on the organisation of care and on the patient's care and life pathway (see 3.5 "Modification of care pathway") due to:
  - the different phases necessary before administration of treatment (mobilisation, apheresis and conditioning),
  - the need for hospitalisation in a protected sector,
  - the administration of treatment in specialised centres only,
  - the need for close coordination between the various departments of centres authorised to treat patients with exagamglogene autotemcel,
  - the usual patient monitoring and management procedures following autologous HSC transplantation,
  - the risk of infertility in men and woman associated with myeloablative conditioning, which should lead to discussion and, if applicable, scheduling of fertility preservation options before treatment,

  which need to be compared with the standard strategy based on life-long, frequent and regular blood transfusions in combination with iron chelation therapy,

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:

- **substantial in the indication "treatment of transfusion-dependent β-thalassaemia (TDT) in patients 12 to 35 years of age for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available",**
- **insufficient to justify public funding in view of the available alternatives in the other MA situations (patients over 35 years of age).**

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 indication "treatment of transfusion-dependent β-thalassaemia (TDT) in patients 12 to 35 years of age for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available" in the list of covered drugs for inpatients approved for use in the MA indication and at the MA dosages.**
- **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 (patients over 35 years of age).**

The Committee makes maintenance of the substantial clinical benefit conditional on reevaluation of the medicinal product within a maximum period of 3 years, based on the additional results requested (see 5.6 Requests for data).

Clinical Added Value

➔ Within the reimbursement scope

Considering:

- the available data demonstrating the efficacy of exagamglogene autotemcel in terms of short-term transfusion independence, which is clinically relevant, with 92.9% of patients having received CASGEVY (exagamglogene autotemcel) achieving transfusion independence for 12 consecutive months (defined by an Hb concentration (weighted mean) ≥ 9 g/dl without transfusion), noting that this percentage was 86.7% taking into account all patients mobilised (3 patients dropped out of the study during the mobilisation phase),

but also considering:

- the preliminary nature of these data, produced from interim analyses on a small number of patients (n=42) followed up for a short period of time, leading to numerous uncertainties, particularly concerning:
  - the maintenance of efficacy and the longer-term safety, particularly the potential tumour risk, in view of the post-treatment median follow-up currently limited to 22.8 months in 54 patients,
  - the evolution of iron overload and its impact on organ damage, which cannot be assessed due to a lack of adequate data,
  - the curative nature of this gene therapy, with the persistence of dyserythropoiesis, which is not corrected in some patients,
  - the difficulties of haematopoietic stem cell mobilisation, sometimes requiring several mobilisation cycles,
- uncertainties with respect to the clinical relevance of the primary endpoint, defined by a target Hb of 9 g/dl (target aimed at before transfusion under standard therapy with regular transfusions), which may be insufficient given that the Hb produced is HbF, which is less effective in terms of release of O2 into the tissues than HbA,
- the lack of comparative data enabling the value of this gene therapy to be assessed in comparison with current management,

the Committee deems that CASGEVY 4 to 13 x 10^6 cells/mL (exagamglogene autotemcel) provides a minor clinical added value (CAV IV) in the current care pathway, which includes the relevant comparators (see 5.2).