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***Title*** ZYNTEGLO – A Health Technology Assessment

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***Reference*** link to full report in French
https://www.has-sante.fr/jcms/p_3149334/fr/zynteglo

**Aim**

Assessment of ZYNTEGLO (betibeglogene autotemcel) with a view to funding by the French national health insurance system, and of its clinical contribution compared to other strategies for the treatment of patients with transfusion-dependent β-thalassaemia (TDT), age 12 years and over, who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

**Conclusions of Transparency Committee**

Clinical Benefit :

- β-thalassaemia is a particularly serious disease that is rapidly life-threatening in the absence of treatment. The age of death of β-thalassaemia patients with current treatment is well below that of the general population, with a severely impaired quality-of-life.
- ZYNTEGLO (betibeglogene autotemcel) is a curative treatment.
- Its efficacy/adverse effects ratio is significant in patients over 12 years and under 35 years of age. It has not been assessed in patients over 35 years of age.
- There is a therapeutic alternative, which is life-long symptomatic treatment (blood transfusions combined with iron chelators).
- ZYNTEGLO (betibeglogene autotemcel) is an alternative to life-long standard symptomatic treatment with blood transfusions combined with iron chelation therapy, only for transfusion-dependent patients over 12 years and under 35 years of age, who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available (see section 08).

ZYNTEGLO can be prescribed on the basis of 2 combined conditions:
1) age: since ZYNTEGLO has only been assessed in patients under the age of 35 years, given uncertainties in terms of its efficacy and safety in older patients, only patients age 12 years up to 35 years may be eligible for ZYNTEGLO treatment. In the absence of any assessment of the clinical benefit in patients aged over 35 years, these patients must not be treated with ZYNTEGLO.
2) treatment history: ZYNTEGLO has only been assessed in patients treated and followed up for at least 2 years in a specialised centre and who are clinically stable. Therefore ZYNTEGLO is not intended to be administered from the outset in a newly diagnosed patient but is aimed only at patients treated and followed up for a period of at least 2 years in a specialised centre and who are clinically stable. ZYNTEGLO is not intended to be administered from the outset in a newly diagnosed patient.
ZYNTEGLO therefore has no role in the care pathway of patients over 35 years of age or as first-line treatment.

- ZYNTEGLO (betibeglogene autotemcel) is likely to have an additional impact on public health.

Considering all of the above, the Committee deems that the clinical benefit of ZYNTEGLO (betibeglogene autotemcel) is:

- substantial only in the treatment of patients over 12 years and under 35 years of age with transfusion-dependent β-thalassaemia (TDT) who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.
- insufficient to justify its funding by the French national health insurance system in the MA indication in patients aged 35 years and over.

Clinical Added Value
Considering:

- the results, considered to be clinically relevant, demonstrating the efficacy of ZYNTEGLO in terms of transfusion independence (primary outcome measure) assessed in 3 open-label, non-comparative studies, only in patients over 12 and under 35 years of age, but,
- numerous uncertainties, concerning in particular:
  - the maintenance of medium and long-term efficacy in view of the maximum follow-up of ZYNTEGLO treatment currently limited to 5 years for a population of only 3 patients,
  - the long-term safety of ZYNTEGLO, particularly with respect to the potential risk of insertional mutagenesis,

ZYNTEGLO (betibeglogene autotemcel) provides moderate clinical added value (CAV III) in the treatment of non β0/β0 genotype patients ≥ 12 years and < 35 years of age with transfusion-dependent β-thalassaemia, for whom HSC transplantation is appropriate but who do not have a matched related donor.

**Recommendations**

The Transparency Committee issued its approval for the funding of ZYNTEGLO (betibeglogene autotemcel) by the French national health insurance system, for use only in the treatment of patients over 12 years and under 35 years of age with transfusion-dependent β-thalassaemia (TDT) who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available, and at the MA dosages.

**Methods**

The assessment of ZYNTEGLO (bétibéglogène autotemcel) was founded on evidence-based medicine with a critical analysis of the clinical data.

**Written by**

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