

# The Medical Letter<sup>®</sup>

## on Drugs and Therapeutics

Volume 66

May 13, 2024

ISSUE No.  
**1702**

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## on Drugs and Therapeutics

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### IN BRIEF

#### Casgevy for Beta Thalassemia

Exagamglogene autotemcel (*Casgevy* – Vertex), a cell-based gene therapy recently approved for treatment of sickle cell disease<sup>1</sup>, has now been approved by the FDA for treatment of patients  $\geq 12$  years old with transfusion-dependent beta thalassemia. *Casgevy* is the first gene therapy that uses CRISPR/Cas9 gene-editing technology to be approved in the US for any disorder. Betibeglogene autotemcel (*Zynteglo*), an autologous lentiviral vector cell-based gene therapy, was approved in the US in 2022 for treatment of transfusion-dependent beta thalassemia.

**THE DISORDER** – Beta thalassemia can cause severe anemia, fatigue, shortness of breath, failure to thrive, jaundice, an enlarged spleen, liver or heart, and delayed puberty. Frequent transfusions and iron chelation therapy have been effective in many patients with transfusion-dependent beta thalassemia; iron overload is a complication of long-term transfusion therapy and can cause significant organ damage. The only definitive cure for beta thalassemia is allogeneic bone marrow transplantation.<sup>2</sup>

**GENE THERAPY** – *Casgevy* is prepared from autologous CD34+ hematopoietic stem cells obtained by mobilization and apheresis. CRISPR/Cas9 gene-editing technology is used to modify the stem cells to reduce BCL11A expression (BCL11A represses fetal hemoglobin) in erythroid lineage cells.<sup>3</sup> The modified stem cells increase production of fetal hemoglobin in red blood cells, reducing the need for transfusions.

**A CLINICAL STUDY** – Approval of *Casgevy* for beta thalassemia was based on the results of an ongoing single-arm trial (CLIMB THAL-111) in 52 patients (only 35 had sufficient follow-up data) 12 to 35 years

old with transfusion-dependent beta thalassemia. Patients were treated with myeloablative conditioning therapy followed by a single dose of *Casgevy*. After a median follow-up of 20.4 months, 91% of patients had achieved transfusion independence for at least 12 consecutive months. All treated patients achieved successful neutrophil and platelet engraftment.<sup>4</sup> A trial evaluating the effects of *Casgevy* for up to 15 years post-infusion is ongoing.

No trials directly comparing *Casgevy* with *Zynteglo* for treatment of beta thalassemia are available, but in 2 unpublished clinical trials (summarized in the *Zynteglo* package insert), rates of transfusion independence achieved with *Zynteglo* were similar to those achieved with *Casgevy*.

**ADVERSE EFFECTS** – *Casgevy* has been associated with neutrophil engraftment failure, delayed platelet engraftment, mucositis, and febrile neutropenia. Myeloablative conditioning therapy can cause significant toxicity and infertility.

**DOSAGE, ADMINISTRATION, AND COST** – A single weight-based dose of *Casgevy* (a minimum of  $3 \times 10^6$  CD34+ cells/kg) is infused between 48 hours and 7 days after myeloablative conditioning therapy. The wholesale acquisition cost (WAC) of a single dose is \$2.2 million for *Casgevy* compared to \$2.8 million for *Zynteglo*.<sup>5</sup> ■

1. Casgevy and Lyfgenia: two gene therapies for sickle cell disease. *Med Lett Drugs Ther* 2024; 66:9.
2. S Ali et al. Current status of beta-thalassemia and its treatment strategies. *Mol Genet Genomic Med* 2021; 9:e1788.
3. H Frangoul et al. CRISPR–Cas9 gene editing for sickle cell disease and  $\beta$ -thalassemia. *N Engl J Med* 2021; 384:252.
4. F Locatelli et al. Exagamglogene autotemcel for transfusion-dependent  $\beta$ -thalassemia. *N Engl J Med* 2024 April 24 (epub).
5. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource<sup>®</sup> Monthly. April 5, 2024. Reprinted with permission by First Databank, Inc. All rights reserved. ©2024. www.fdbhealth.com/drug-pricing-policy.

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