NOTIFICATION TO THE EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the European Medicines Agency made by the European Commission (EC):

Product Name	ZYNTEGLO
Active substance	Genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the βA-T87Q-globin gene.
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	bluebird bio (Netherlands) B.V.

ZYNTEGLO (betibeglogene autotemcel) is a genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the βA-T87Q-globin gene.

It was authorised in the EU on 29 May 2019 for the treatment of patients 12 years and older 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.

The product is currently used in one centre in the EU, and only one patient has been treated since granting of the marketing authorisation outside of clinical studies.

On 15 February 2021 the EMA received information from the marketing authorisation holder of ZYNTEGLO informing about an adverse event in a sickle cell disorder (SCD) patient treated in a clinical study with an investigational medicinal product (bb1111) for treatment of SCD, which uses the same lentiviral vector to transduce CD34+ cells.

After about 5 years, the relative frequency of βA-T87Q-globin gene transduced peripheral blood cells with integration in the VAMP4 locus increased significantly. The patient was diagnosed with acute myeloid leukaemia (AML) about 5.5 years after the treatment with bb1111.

Some of the characteristics of the patient's adverse event (time to onset, presence of lentiviral integration in AML blast cells) occurring after exposure to bb1111 thus raise concerns regarding a possible causal association between the lentiviral vector or other aspects related to the therapy and the event.

The marketing authorisation holder also reported two cases of myelodysplastic syndrome (MDS) after use of bb1111 that occurred in the same study.

In view of the above it is therefore necessary to review all available data to investigate a potential causal relationship between the use of the lentiviral vector in the investigational product bb1111 and ZYNTEGLO and the occurrence of clonal disorders, especially regarding the impact of lentiviral integration (in CD34+ or other cells) on oncogenic driver mutations, other aspects related to the therapy and the potential impact for patients receiving ZYNTEGLO.

In view of the above, the European Commission initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product ZYNTEGLO, which is formulated with the same lentiviral vector as the investigational product bb1111.

The European Commission requests the Agency to give its opinion as soon as possible and by 30 September 2021 at the latest on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

In addition, the European Commission requests the Agency to give its opinion, as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of this medicinal product.

[E-signed]

Signed Date 18/02/2021

Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General