

## Direct Healthcare Professional Communication

18 March 2021

### **Zolgensma (onasemnogene abeparvovec): risk for thrombotic microangiopathy**

Dear Healthcare Professional,

Novartis Gene Therapies EU Limited in agreement with the European Medicines Agency and <National Competent Authority> would like to inform you of the risk for thrombotic microangiopathy (TMA) following Zolgensma (onasemnogene abeparvovec) treatment.

#### **Summary**

- **Thrombotic microangiopathy (TMA) has been reported in spinal muscular atrophy (SMA) patients treated with onasemnogene abeparvovec, particularly in the first weeks following the treatment.**
- **TMA is an acute and life-threatening condition characterised by thrombocytopenia, haemolytic anaemia and acute kidney injury.**
- **Creatinine and complete blood count (including haemoglobin and platelet count) testing is now required before administration of onasemnogene abeparvovec in addition to the currently recommended baseline laboratory testing.**
- **Platelet counts should be closely monitored in the week following infusion and on a regular basis afterwards. In case of thrombocytopenia, further evaluation including diagnostic testing for haemolytic anaemia and renal dysfunction should be undertaken.**
- **If patients exhibit signs, symptoms or laboratory findings suggestive of TMA, direct specialist and multidisciplinary advice should be sought and TMA should be immediately managed as clinically indicated.**
- **Caregivers should be informed about signs and symptoms of TMA (e.g. bruises, seizures, oliguria) and should be advised to seek urgent medical care if such symptoms occur.**

#### **Background on the safety concern**

Zolgensma (onasemnogene abeparvovec) is indicated for the treatment of spinal muscular atrophy (SMA). The overall cumulative exposure is approximately 800 patients to date.

TMA represents a diverse group of conditions, which includes haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The incidence of TMA in children overall is estimated to be only a few cases/million/year.

TMA is diagnosed by the presence of thrombocytopenia, haemolytic anaemia, and acute kidney injury, and occurs due to dysregulation and/or excessive activation of the alternative complement pathway. Its aetiology can be genetic or acquired. TMA is treatable and can resolve with timely and proper interventions. It is important to have increased awareness of TMA for patients receiving onasemnogene abeparvovec.

In total, five confirmed cases of TMA in patients aged 4-23 months have so far been reported after treatment with onasemnogene abeparvovec, among approximately eight hundred treated patients.

In these five cases, TMA developed within 6-11 days after onasemnogene abeparvovec infusion. The presenting features included vomiting, hypertension, oliguria/anuria, and/or oedema. Laboratory data revealed thrombocytopenia, elevated serum creatinine, proteinuria and/or haematuria, and haemolytic anaemia (decreased haemoglobin with schistocytosis on peripheral blood smear). Two of the patients also had infections, and both of them had recently (within 2-3 weeks after onasemnogene abeparvovec administration) been vaccinated. Information on how to schedule administration of vaccinations with Zolgensma is described in the product information.

In the acute phase, all patients responded well to medical interventions including plasmapheresis, systemic corticosteroids, transfusions and supportive care. Two patients underwent renal replacement therapy (haemodialysis or haemofiltration). Unfortunately one patient who required renal replacement therapy (haemofiltration) died 6 weeks after the event.

The product information for onasemnogene abeparvovec will be updated to reflect the risk of TMA, and to provide monitoring advice for timely recognition of TMA as well as advice to inform the caregivers about the need to seek urgent medical care if signs and symptoms of TMA occur.

### ***Call for reporting***

Please report any suspected adverse reactions associated with the use of onasemnogene abeparvovec in accordance with the national requirements via the national spontaneous reporting system, to:

<Details of national reporting systems as per Appendix V to be included prior to submission to national MS Competent Authorities>

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

▼ Zolgensma is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions as soon as possible.

### ***References***

Bérangère S, Joly, X, Long Zheng, et al (2018). Understanding thrombotic microangiopathies in children. *Intensive Care Med.*, Sep;44(9):1536–1538.

Chand DH, Zaidman C, Arya K, Millner R, Farrar MA, Mackie FE, Goedeker NL, Dharnidharka VR, Dandamudi R, Reyna SP. Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: A Case Series. *J Pediatr.* 2020

Nov 28:S0022-3476(20)31466-9. doi: 10.1016/j.jpeds.2020.11.054. Epub ahead of print. PMID: 33259859.

Kaplan BS, Ruebner RL, Spinale JM, et al. Current treatment of atypical hemolytic uremic syndrome. *Intractable Rare Dis Res*. 2014;3(2):34–45.

Joly BS, Zheng XL, Veyradier A. Understanding thrombotic microangiopathies in children. *Intensive Care Med*. 2018;44(9):1536–1538.

Wijngaarde CA, Huisman A, Wadman RI, et al. Abnormal coagulation parameters are a common non-neuromuscular feature in patients with spinal muscular atrophy. *J Neurol Neurosurg Psychiatry*. 2020;91(2):212–214.