Direct Healthcare Professional Communication

18th 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 the Medicines and Healthcare products Regulatory Agency (MHRA) 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 onasemnogne 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 continue to report suspected adverse drug reactions (ADRs) associated with the use of onasemnogene abeparvovec to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

You can report via:

- the Yellow Card website www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, investigation results, treatment dates, and product brand name.

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.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com.

Company contact point

If you have any questions regarding Zolgensma, please contact:

Novartis Gene Therapies EU Ltd (UK branch)

Medical Information at Tel: +44 20 7949 4555 or MedinfoEMEA.gtx@novartis.com

General enquiries at Tel: +44 20 3580 4484

Yours faithfully,

Dr Imran Kausar MBChB, MRCA

Medical Director

Novartis Gene Therapies UK

References

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