Direct Healthcare Professional Communication

31st July 2018

Spinraza▼ (nusinersen): reports of communicating hydrocephalus not related to meningitis or bleeding

Dear Healthcare Professional,

Biogen, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of the following:

Summary

- **Communicating hydrocephalus not related to meningitis or bleeding has been reported in patients, including children, treated with Spinraza. Some of them were managed with implantation of a ventriculo-peritoneal shunt (VPS).**
- **Patients and caregivers should be informed about the signs and symptoms of hydrocephalus before Spinraza is started and should be instructed to seek medical attention in case of: persistent vomiting or headache, unexplained decrease in consciousness, and in children increase in head circumference.**
- **Patients with signs and symptoms suggestive of hydrocephalus should be further investigated by a physician with expertise in its management.**
- **In patients with decreased consciousness, increased CSF pressure and infection should be ruled out.**
- **There is limited information on the continued effectiveness of Spinraza when a VPS is implanted. Physicians should closely monitor and assess patients who continue to receive Spinraza following placement of a VPS.**
- **Patients and caregivers should be informed that the risks and benefits of Spinraza in patients with a VPS are not known.**

Background on the safety concern

Spinraza is a medicine indicated for the treatment of 5q spinal muscular atrophy (SMA). Following an initial regimen of four loading doses over a course of 63 days, it is administered every 4 months. Spinraza is administered intrathecally by lumbar puncture.

Communicating hydrocephalus, not related to meningitis or bleeding, has been reported in patients, including children, with SMA treated with Spinraza.

Given the potential consequences of untreated hydrocephalus, Biogen is alerting physicians involved in the care of SMA patients (such as neurologists and neuro-paediatricians) to the potential risk for communicating hydrocephalus associated with Spinraza treatment. Physicians are advised to discuss

this potential risk with patients and caregivers and advise them to be vigilant about signs and symptoms of hydrocephalus.

An evaluation for hydrocephalus should be considered in patients with signs or symptoms of hydrocephalus, including persistent vomiting or headache, unexplained decrease in consciousness, and, in children, an increase in head circumference. Physicians should closely follow any patient that presents with concerning signs or symptoms. Patients diagnosed with hydrocephalus should be promptly referred to a physician with expertise in its management.

In patients with SMA, management of hydrocephalus has included placement of a ventriculo-peritoneal shunt (VPS). At least two of the children who developed communicating hydrocephalus whilst being treated with Spinraza were managed with implantation of a VPS. There is limited information on the continued effectiveness of Spinraza when a VPS is implanted.

Physicians are advised to closely monitor and assess patients who continue to receive Spinraza following placement of a VPS. Patients/their caregivers should be informed that the risks and benefits of Spinraza in patients with a VPS are not known.

Short descriptions of five cases reported up to 6 July 2018:

A 4-month-old female with Type I SMA who had received three doses of Spinraza presented with enlarging head size and lethargy, and was diagnosed with communicating hydrocephalus. Results from a CSF sample showed no evidence of an infection. The patient underwent placement of a VPS. The patient continues to receive Spinraza therapy.

A 6-month-old male with Type I SMA who had received four doses of Spinraza exhibited signs of increased intracranial pressure with nystagmus and tense fontanelle. Communicating hydrocephalus with markedly enlarged inner CSF spaces was shown. Spinal magnetic resonance imaging did not show evidence of space occupying lesions or bleeding. A VPS was placed. The patient continues to receive Spinraza therapy.

A 3-year-old male with Type I SMA had received two doses of Spinraza when brain MRI revealed communicating hydrocephalus. There was no treatment administered for the hydrocephalus, but the patient is being followed by a neurosurgery clinic. Treatment with Spinraza was discontinued.

A 5-month-old male with Type I SMA who received four doses of Spinraza presented with macrocephaly and was diagnosed with communicating hydrocephalus. Results of a CSF sample showed no evidence of infection. As treatment, the patient has an external ventricular drain (EVD) and is awaiting VPS. The patient is planned for continued Spinraza therapy.

An adult female patient with SMA who had received Spinraza was diagnosed with communicating hydrocephalus. The patient was reported to also have scoliosis.

The Summary of Product Characteristics (SmPC) and Package Leaflet of Spinraza will be updated to reflect this new warning and precaution.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) 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▼

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line:

  0800-731-6789 or
- by downloading and printing a form from the yellow card website (see link above)

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

Company contact point

Further information can be requested from Biogen by telephone (0800 008 7401), fax [+44 (0) 1628 501 010] or email (MedInfoUKI@biogen.com).

Annexes

Contact point details for further information are given in the product information of the medicinal product (SmPC and PIL) at http://www.medicines.org.uk/emc.

Yours faithfully

Dr Simon Beck
Medical Director, UK and Ireland

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