Medicines & Healthcare products
Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

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MHRA

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09 October 2018

Dear Ms Hassell,

Reference: regulation 28: Prevention of Future Deaths report – Collin Gary Griffiths

Thank you for copying to the MHRA, your report dated 4 September 2018, under paragraph 7, schedule 5, of the Coroners and Justice Act 2009 and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013, concerning the death of Mr. Collin Gary Griffiths.

Further to the information provided on this tragic case, we have considered whether the statutory information currently provided by the marketing authorisation holders for prescribers (and patients) on the safe use of this vaccine is adequate, and whether any other regulatory measures could be taken to minimise the risk of yellow fever vaccine-associated viscerotropic disease in those for whom the vaccine is contraindicated.

Information on the use of medicines is provided to healthcare professionals through the Summary of Product Characteristics (SmPC) and to patients through the Patient Information Leaflet (PIL). Full details of the SmPCs and PILs may be found on the MHRA's website (http://www.mhra.gov.uk/spc-pil/), and the electronic medicines compendium (https://www.medicines.org.uk/emc/)

The following recommendations are provided in the yellow fever vaccine (Stamaril) SmPC:

- Section 4.3 (contraindications) –

  History of thymus dysfunction (including myasthenia gravis, thymoma, thymectomy);
  Immunosuppression, whether congenital, idiopathic or as a result of treatment with systemic steroids (greater than the standard dose of topical or inhaled steroids), radiotherapy or cytotoxic drugs.

- Section 4.4 (warnings and precautions) –

  Before considering administration of yellow fever vaccine, care should be taken to identify those who might be at increased risk of adverse reactions following vaccination (see Section 4.3 and below).

Very rarely, Yellow Fever Vaccine-Associated Viscerotropic Disease [YEL-AVD] resembling fulminant infection by wild-type virus has been reported following vaccination (see Section 4.8). The mortality rate has been around 60%. To date, most of cases of YEL-AVD have been reported in primary vaccinees with an onset within 10 days of vaccination. The risk appears to be higher in those aged over 60 years although cases have also been reported in other age groups. History of thymus dysfunction has also been recognized as a potential risk factor (see Section 4.3).

STAMARIL must not be administered to immunosuppressed persons (see Section 4.3).

- Section 4.8 (undesirable effects) –

Cases of viscerotropic disease (known as yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and formerly described as "Febrile Multiple Organ-System Failure") have been reported following vaccination with yellow fever vaccines, some of which have been fatal. In the majority of cases reported, the onset of signs and symptoms was within 10 days after the vaccination. Initial signs and symptoms are non-specific and may include pyrexia, myalgia, fatigue, headache and hypotension, potentially progressing quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia and acute respiratory and renal failure (see Section 4.4). YEL-AVD is listed as an undesirable effect that may occur very rarely (at a frequency of <1/10,000).

The Patient Information Leaflets for the yellow fever vaccine provides the following recommendations:

- Patients should inform their doctor or nurse if they have a history of problems with their thymus gland or have had their thymus gland removed for any reason.
- A serious reaction affecting vital organs occurring within 10 days of vaccination is mentioned as a possible side effect, that can have a fatal outcome, with the yellow fever vaccine. The reaction can resemble an infection with the yellow fever virus and the signs may include: feeling tired, fever, headache, muscle pain and sometimes low blood pressure. It may then go on to a severe muscle and liver disorder, drops in number of some types of blood cells resulting in unusual bruising or bleeding and increased risk of infections, and loss of normal functioning of the kidneys and lungs.

On review of this information, and in relation to actions within the remit of the MHRA, we are satisfied that the statutory SmPC and PIL for yellow fever vaccine provides relevant contraindications and warnings to minimise the risk of use in those with a history of thymus dysfunction. The general view of the MHRA (in relation to all vaccines and medicines) is that PILs should be provided to patients, parents or vaccinees when a vaccine or medicine is given, and that provision of the PIL would also be valuable as part of the informed consent process and discussions with patients about the benefits and risks of their vaccines and medicines. All PILs now also carry information on how to report possible side effects to the MHRA, and patients, parents or vaccinees should be made aware of this mechanism.

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As you are aware, yellow fever vaccine is a live vaccine, containing a small amount of attenuated (weakened) virus which mimics a natural infection. Live attenuated vaccines should not be given to people who are clinically immunosuppressed due to the risks of over-replication of vaccine virus. You may wish to be aware that, following other recent reports of fatal events in immunocompromised patients who inadvertently received live shingles vaccine, the MHRA issued a reminder of this general risk of live vaccines to healthcare professionals via its Drug Safety Update (DSU) bulletin in April 2016: https://www.gov.uk/drug-safety-update/live-attenuated-vaccines-avoid-use-in-those-who-are-clinically-immunosuppressed. As there have now been three fatal cases reported to us we intend to issue a further reminder about the risks of live vaccines in immunocompromised patients, including Yellow Fever vaccine in Drug Safety Update.

Finally, for your reference the report of Mr Griffiths' adverse reaction to Yellow Fever vaccine has been added to the MHRA's Yellow Card database with the reference ADR 23432502.

Yours sincerely,

Dr Ian Hudson
Chief Executive
Medicines and Healthcare products Regulatory Agency