



Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system and requirements for reporting safety data

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. In some cases, the safety profile of the EAMS medicine may not yet be fully established and it is therefore particularly important that any harmful or unintended responses to EAMS medicines are reported. More information about the scheme can be found here:

<http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

Healthcare professionals should enroll any patients receiving EAMS medicines in the registry which the pharmaceutical company will have in place to enable systematic collection of information on adverse events.

Suspected adverse drug reactions (ADRs) for any patients, particularly those not enrolled in a study (or registry), can be reported directly to the MHRA via the Yellow card scheme at www.mhra.gov.uk/yellowcard.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, outcome and results of any test results or investigations. Alternatively, healthcare professionals can report ADRs which occur in patients not enrolled in any study (or registry) directly to the pharmaceutical company who manufactures the EAMS medicine.

The information below is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. The description below summarises the requirements for clinical monitoring and reporting of adverse events with medicines used under the scheme.

Prescribing doctors should also consult the relevant detailed information provided by the company.

EAMS indication:

Avelumab in combination with axitinib for use in treatment-naïve patients with advanced renal cell carcinoma.

Information on the Pharmacovigilance system:

A prescribing oncologist requests entry of their patients into the Early Access to Medicines Scheme (EAMS) via an online portal (<https://portal.inceptua.com/#/login>) by completing a patient access form.

Upon successful registration on the EAMS, each prescribing oncologist will be provided with an electronic version of the physician's pack containing the following documents:

- Patient Access Form to make first drug order and subsequent re-supply requests
- EAMS Treatment Protocol – Information on the pharmacovigilance system and requirements for reporting safety data (this document)
- EAMS adverse event reporting form
- EAMS Treatment Protocol – Information for Healthcare Professionals
- EAMS Treatment Protocol – Information for Patients
- Patient Informed Consent form
- Information for Patients Brochure
- Patient Alert Card
- EAMS Protocol number: 11648-0002-01

Active Pharmacovigilance:

All HCPs (physicians, pharmacists and nurses) involved with the EAMS will be directed to report all adverse events (serious and non-serious), any exposure during pregnancy (including exposure from male participants of the EAMS) and lactation, lack of efficacy, occupational exposure, transmission of infectious agents, off label use or unintended drug exposure via caregiver, medication errors, overdose, misuse or abuse, drug interactions or unexpected benefit within 24 hours to Merck UK Pharmacovigilance, as specified in the relevant documentation in the physician's pack. Confirmation of understanding for reporting provisions shall be provided to Merck before commencement of treatment.

Patients/caregivers will be trained by the EAMS Physicians to recognise and document adverse events. Training will be provided at the time the patient enters the EAMS programme.

NHS England will allocate each patient a unique identifier upon enrolment into the EAMS program for renal cell carcinoma (RCC). This will allow tracking of patients from baseline and throughout the treatment period. Merck shall allocate a number for patients enrolled from devolved nations. This will also be used for monitoring safety information as necessary.

Patients/caregivers will be instructed to contact their EAMS physician immediately if they experience any adverse events.

A 3-monthly periodic safety report will be submitted to the MHRA to summarize data on safety and usage of avelumab (in combination with axitinib) under the scheme.

The Merck UK Pharmacovigilance team will collect additional information including pregnancies, treatment discontinuation and/or product complaints from the participating centres. These will be recorded on the EAMS AE form. All AEs will be notified to Merck UK Pharmacovigilance by the EAMS physician within 24 hours. The Merck UK Pharmacovigilance team will follow up on all SAEs and special situation information received in an expedited manner.

In accordance with Merck pharmacovigilance procedures, all AEs received by Merck UK pharmacovigilance will be validated, assessed for causality and related AEs will be reported to the MHRA within 15 calendar days of day zero, if assessed as serious according to criteria for serious AEs, as per ICH E2D, i.e. any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect or according to important medical events. Of particular note, all events that are assessed as suspected due to the medicine and unexpected

that have resulted in a fatal outcome, will be reported to the MHRA within 7 calendar days. All other AEs with fatal outcomes will be reported within 15 calendar days. Non-serious AEs shall be reported accordingly within 90-days.

If appropriate, all reports will be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. The data management of all AE/safety information will be in accordance with Merck's pharmacovigilance procedures. Merck will prepare pharmacovigilance progress reports using descriptive analysis. These reports will be provided to the MHRA every 3 months.

Training for Healthcare Professionals (HCPs)

All HCPs involved with the management of the EAMS will receive training from Merck/Pfizer in addition to the information they receive in the physician's pack upon set up. The Merck UK medical team will provide training upon receipt of positive scientific opinion from the MHRA. This will include a presentation of key clinical data, product information, AE reporting and logistics of the EAMS. Additionally, the HCP will be trained on further additional risk minimisation measures including a patient alert card and an information for patients brochure. To reaffirm the importance of reporting obligations, a reminder shall also be provided and inserted accordingly at the point of product ordering.

The training will focus particularly to recognising, managing and reporting adverse events.

As part of this training, the HCP receives and will be asked to provide the Information for Patients Brochure and a Patient Alert Card to each patient at initiation of their treatment (see below). HCPs will also be trained in how to train patients/caregivers to manage and report adverse events.

Information for Patients Brochure and Patient Alert Card:

This brochure and card will be given to all patients before they start treatment. The brochure covers immune related adverse events, to educate patients on the characteristic signs and symptoms. The alert card is a wallet-sized card to be carried to show at all medical visits to HCPs other than the treating physician (e.g. emergency HCP's). The card has contact details of the treating physician and alerts other physicians that the patient is treated with avelumab. It also contains information on the main symptoms of the important adverse reactions and highlights the importance of notifying the treating physician immediately if symptoms occur, persist or worsen and also the importance of not attempting to self-treat any symptoms without consulting with an HCP first.

Additional information:

All HCP and patient registration, alongside drug supply shall be recorded via an online portal (<https://portal.inceptua.com/#/login>). All relevant patient baseline characteristics (as described in section 7 of the EAMS protocol), alongside confirmation that the patient is suitable for the EAMS including Demography (age and gender), Eastern Cooperative Oncology Group Performance Status (ECOG-PS 0-1) and International Metastatic Renal Cell Carcinoma (IMDC) risk score. Confirmation that the patient has advanced Renal Cell Carcinoma, Contraception/pregnancy check (female subjects of childbearing potential), Urine pregnancy test (female subjects of childbearing potential), Weight and Unique EAMS identification number shall be completed to register a patient and to enable access to the EAMS drug supply.

To enable further supply of the EAMS drugs, HCPs will need to confirm that patients are still suitable for treatment and that all AEs have been reported. Upon successful registration and first request of EAMS drug supply, 2 cycles (8 weeks) of avelumab and axitinib will be supplied. A request for re-supply would need to be made for every subsequent re-order.

Contact details:

Contact details for reporting AEs: 0208-818-7373

Email Address: ICSR_UKI@merckgroup.com

Telephone Contact: Merck Medical Information number (including out of hours): 0208-818-7373

Contact email for Merck Medical Information: medinfo.uk@merckgroup.com

Contact email for the EAMS programme: eams@merckgroup.com