Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Avelumab 20 mg/mL concentrate for solution for infusion**
EAMS indication	**Avelumab is used to treat adult patients with urothelial carcinoma (a type of bladder cancer) when it is advanced (has spread beyond the bladder) if the cancer did not get worse after an initial course of chemotherapy (including a platinum drug)**
Company	**Merck Serono Limited**
EAMS number	**11648/0003**
EAMS Scientific Opinion date	**01/09/2020**

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

The General Medical Council's guidance on prescribing unlicensed medicines can be found here:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is avelumab?

Avelumab is the active substance of a medicine, which is given by infusion via a drip into a vein. It is supplied as a concentrated solution for dilution in an infusion bag containing a sodium chloride solution before use.

What is avelumab used to treat?

Avelumab is used to treat adult patients with urothelial carcinoma (a type of bladder cancer) when it is advanced (has spread beyond the bladder) if the cancer did not get worse after an initial course of chemotherapy (including a platinum drug).

How is avelumab used?

Treatment with avelumab should be started and supervised by a specialist doctor who is experienced in the treatment of cancer. The doctor will carry out blood tests before and during treatment to monitor the patient. Avelumab will be given in a hospital or clinic.

Avelumab treatment is used as monotherapy, that is, it is not combined with other anti-cancer medicines.

A dose of 800 mg is given by infusion into a vein over a period of one hour. This is repeated every 2 weeks until the cancer gets worse (progresses), or unacceptable side-effects occur. The dose is not adjusted in patients ≥65 years of age, patients with mild or moderate kidney problems and patients with mild liver problems. There is not enough evidence to recommend the use of avelumab in children and adolescents below the age of 18 years.

Patients will be given paracetamol and an antihistamine medicine before receiving avelumab to reduce the risk of reactions to the infusion. If a reaction occurs, the infusion will be slowed down or stopped.

Avelumab can cause certain side effects due to stimulation of the immune system. If these side effects occur, avelumab treatment may be interrupted or permanently discontinued, depending on the severity of the side effect.

How does avelumab work?
Avelumab is a monoclonal antibody (a type of protein) that attaches to a specific target in the body called programmed death-ligand 1 (PD-L1). PD-L1 is found on the surface of certain tumour cells and helps protect them from the immune system. Avelumab binds to PD-L1, and blocks this protective effect, allowing the immune system to attack the tumour cells.

How has avelumab been studied?
A total of 700 adult patients with advanced urothelial carcinoma were enrolled into a study that compared avelumab (in addition to usual care) with usual care alone. The study patients had already received one course of chemotherapy (including a platinum drug) for advanced urothelial carcinoma. This was completed 4 to 10 weeks before the start of the study. Patients whose cancer progressed after chemotherapy, as shown by a scan, were excluded from the study.

Half of the study patients received avelumab in addition to usual care and half received usual care alone. Study treatment was decided randomly by a central computer. Study patients were followed-up with regular visits and scans and monitored for side effects. Avelumab was stopped if side effects were unacceptable, or if the tumour grew.

The main measure of efficacy (how well the medicine worked) was overall survival (how long the patients lived). Another important measure of efficacy was progression-free survival (how long the patients lived without their cancer getting worse). Patients were asked to report bladder cancer symptoms, day-to-day functioning, health status and quality of life, using questionnaires (patient-reported outcomes).

What are the benefits and risks of avelumab?

Benefits
The study results showed that avelumab prolongs overall survival. After 12 months, the estimated overall survival rate was 71% in patients receiving avelumab, compared to 58% in patients receiving usual care alone. Avelumab also prolonged progression-free survival. After 6 months, the estimated rate of progression-free survival was 41% in patients receiving avelumab, compared to 22% in patients receiving usual care alone. There were no differences between avelumab and usual care alone for patient-reported outcome scores.

Risks
Very common side effects (may affect more than 1 in 10 people) are: infection of the bladder, blood in the urine; decrease in the number of red blood cells; itching, rash; nausea, loose stools, constipation,

vomiting, belly pain; back pain, joint pain; cough, shortness of breath; feeling tired or weak; fever; swelling in the arms, feet or legs; weight loss, feeling less hungry; underactive thyroid gland.

Infusion-related reactions are also very common. Symptoms include shortness of breath, wheezing, chills, rash, flushing, dizziness, fatigue, nausea, fever, back pain and abdominal pain.

Serious side effects are caused by stimulation of the immune system. This can cause inflammation in parts of the body including the lungs, liver, large bowel, pancreas, muscles, kidneys and hormone-producing glands. Immune-related side-effects may lead to death and need treatment, or withdrawal of avelumab. Serious infusion-related reactions can occur.

Why has avelumab been given a positive Early Access to Medicine Scientific opinion?
Advanced urothelial carcinoma is a life-threatening condition with a 5-year survival rate of less than 5%. There is an unmet need for treatments to maintain the benefit of chemotherapy and prolong survival. Based on the study results, avelumab in addition to usual care has been shown to prolong overall survival, and progression-free survival, when compared to usual care alone. Patient-reported outcomes did not show that avelumab has a worse effect on bladder cancer symptoms, day-to-day functioning, health status and quality of life. The risks associated with avelumab can be managed and do not outweigh the benefits.

What are the uncertainties?
Information is missing regarding safety in patients with autoimmune disease and those whose immune systems may not work properly due to an underlying condition or a treatment for an underlying condition. There is not enough evidence to recommend a dose in patients with severe kidney problems or patients with moderate or severe liver problems. The company that makes avelumab will provide additional information when it becomes available.

Are there on-going clinical studies?
There is no on-going study of avelumab in the EAMS indication.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that avelumab is used as safely as possible. Based on this plan, the company that make avelumab must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicines including the side effects and recommendations for minimising these side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report side effects experienced by patients receiving avelumab through the scheme. To assist with this, they will receive a physician pack and training prior to commencement of patient treatment. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Patients in the Early Access to Medicines Scheme will receive an information brochure and alert card from their doctor summarising the important immune-related risks with avelumab and the details of their treating oncologist. Patients should carry the alert card with them at all times in case they need treatment or advice from a healthcare professional who is not familiar with avelumab treatment.

Other information about avelumab – see EAMS Treatment Protocol