

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	Avelumab
Condition	Cancer of the kidney that has spread locally, outside of the kidney or distantly to other parts of the body (metastasized)
Full indication	Avelumab in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
Company	Merck Serono Ltd
EAMS number	11648/0002

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to doctors who may wish to prescribe the unlicensed 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 the information supplied to the MHRA on the benefits and risks of a promising new 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. The General Medical Council's guidance on prescribing unlicensed medicines can be found here:

<https://www.gmc-uk.org/ethical-guidance/ethical-hub/trans-healthcare#prescribing>

What is avelumab?

Avelumab is the active ingredient of a medicine and is available as a concentrated solution (liquid) that is diluted for infusion (drip) into a vein.

What is avelumab used to treat?

Avelumab is used in adults to treat advanced renal cell carcinoma, a type of kidney cancer that has spread locally outside of the kidney or distantly to other parts of the body. It is used in combination with axitinib, another cancer therapy which is available as tablets, when no other specific treatments have been given for this stage of the disease.

How is avelumab in combination with axitinib used?

Avelumab is given by a slow injection (infusion) into a vein over 60 minutes at a dose of 800mg every two weeks. To help reduce the risk of a reaction to the infusion, paracetamol and an antihistamine are given before avelumab for at least the first four treatments.

Axitinib tablets (5mg) are taken twice daily (12 hours apart) with or without food.

Avelumab and axitinib treatment is continued unless there is disease worsening or there are intolerable side effects.

How does avelumab work?

Avelumab is a type of protein, called a monoclonal antibody. A monoclonal antibody is a type of protein that has been designed to recognise and attach to a specific structure (called an antigen) that

is found in certain cells in the body. Avelumab has been designed to attach to and block the activity of a protein called PD-L1, which is found on the surface of tumour and immune cells. By blocking PD-L1, avelumab restores the capacity of immune cells to fight cancer cells.

How does axitinib work?

Axitinib blocks some enzymes known as tyrosine kinases that are found on the surface of cancer cells and works by reducing the blood supply to the tumour and slowing down the growth of cancer.

How has avelumab been studied?

The main study compared treatment with avelumab given with axitinib to standard anticancer treatment with sunitinib (another tyrosine kinase blocking agent) given alone in patients who had not previously received treatment for kidney cancer. A total of 886 patients were entered into the study; of these patients, 560 had a tumour that contained PD-L1 (PD-L1 positive).

The study looked at whether patients given the combination of avelumab and axitinib had a longer time until their kidney cancer worsened, compared with patients given sunitinib. This outcome is called progression-free survival (PFS). Other measures of how well the medicines worked were the overall response rate (the proportion of patients whose tumour shrank by over 30% by radiological imaging) and overall survival (how long the patients lived).

What are the benefits and risks of avelumab?

Benefits

Avelumab in combination with axitinib prolonged the time that patients lived without their disease getting worse. After 12 months, the proportion of patients without progression of disease was 53% in the group of patients treated with avelumab and axitinib compared to 41% in those treated with sunitinib. The PFS result was similar for all patients recruited to the study regardless of whether their tumours contained PD-L1 or not.

The proportion of patients who responded to the combined treatment of avelumab and axitinib was higher than those who responded to sunitinib; the overall response rate was 51% with avelumab and axitinib compared to 25% with sunitinib.

Risks

Almost all patients experienced a side effect with avelumab and axitinib. The most common side effects, affecting at least 30% of patients, were diarrhoea, hypertension, fatigue, nausea and a hoarse voice. Severe side effects were frequent, particularly high blood pressure (26%), diarrhoea and increased liver function tests.

Avelumab in combination with axitinib may be associated with side effects resulting from excessive activity of the immune system; most resolved following initiation of appropriate medical therapy or withdrawal of avelumab. Immune-related side effects were most commonly thyroid disorders (inflammation of the thyroid) (25% patients), hepatitis (inflammation of the liver), rash, colitis (inflammation of the intestine) and pneumonitis (inflammation of the lungs). Out of 489 patients treated with avelumab in combination with axitinib in kidney cancer, there were two fatal cases of myocarditis (inflammation of the heart) and two of pancreatitis (inflammation of the pancreas).

Why has avelumab been given a positive Early Access to Medicine Scientific opinion?

Renal cell carcinoma (RCC) is the most common form of kidney cancer. When it has spread, the survival rate at 5 years in the UK is around 56%. Despite the substantial improvements in the treatment of kidney cancer, long lasting and complete tumour shrinkage are uncommon. The combination of avelumab and axitinib has been shown to notably slow the progression of cancer

compared to standard current treatment in patients with good predicted outcome as well as those with poor predicted outcome.

What are the uncertainties?

The data on overall survival are preliminary, most patients were alive at the time of the data analysis and so it is too early to conclude whether avelumab with axitinib combination treatment prolongs overall survival compared to sunitinib.

Long-term safety data for the avelumab with axitinib combination are not yet available. The two fatal cases of myocarditis (inflammation of the heart) and two fatal cases pancreatitis (inflammation of the pancreas) were seen only in patients treated with combination therapy.

Are there on-going clinical studies?

The main study previously described is ongoing. The companies that make avelumab and axitinib will provide additional information when it becomes available.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that avelumab in combination with axitinib are used as safely as possible. Based on this plan, the companies that make avelumab and axitinib 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 companies to report side effects experienced by patients receiving avelumab in combination with axitinib 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 companies.

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 when treated in combination with axitinib 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