Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**isatuximab**
Condition	**Relapsed and refractory multiple myeloma**
Full indication	**Isatuximab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma only if they have received 3 previous lines of therapies (that have included lenalidomide and a proteasome inhibitor) and have demonstrated disease progression on the last therapy.**
Company	**Aventis Pharma**
EAMS number	**04425/0002**
EAMS Scientific Opinion date	**02/12/2019**

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 isatuximab?
Isatuximab is an immunoglobulin IgG1 monoclonal antibody that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation (CD)38. CD38 is expressed in a number of haematological malignancies.

What is isatuximab used to treat/diagnoses/prevent?
Isatuximab is used to treat multiple myeloma (MM), a malignant plasma cell disease that is characterised by clonal proliferation of plasma cells in the bone marrow (BM) and the production of excessive amounts of a monoclonal immunoglobulin. According to Cancer Research UK, MM accounts for 1-2% of all cancers, affecting approximately 17,500 patients in the UK at any one time and in 2016, there were 4,731 people diagnosed with MM in England (Office for National Statistics, 2016). It is a disease predominantly associated with advancing age with more than 80% of patients aged 60 years or older. MM is more common in men than in women and the incidence is also reported to be higher in people of African family origin.

How is isatuximab used?
Isatuximab is administered as an intravenous infusion in combination with pomalidomide and dexamethasone according to the following schedule:

Isatuximab dosing schedule in combination with pomalidomide and dexamethasone

Cycles	Dosing schedule
Cycle 1	Days 1, 8, 15 and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

How does isatuximab work?
Isatuximab is an IgG1 monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on multiple myeloma cells.

Isatuximab acts through IgG Fc-dependent mechanisms including antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism.

How has isatuximab been studied?
The efficacy and safety of isatuximab in combination with pomalidomide and low-dose dexamethasone were evaluated in a multicentre, multinational, randomised, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. The primary efficacy endpoint was progression free survival (PFS). A statically significant increase in PFS, as assessed by an Independent Review Committee, was observed in patients treated with the isatuximab regimen and the primary endpoint was therefore met.

The pharmacokinetics of isatuximab have also been investigated in multiple myeloma patients treated with isatuximab IV as single agent or in combination with pomalidomide and dexamethasone in several phase I studies. The pharmacokinetic data were considered satisfactory.

Isatuximab has not been formally studied in patients with hepatic or renal impairment, or in patients under 18 years of age.

What are the benefits and risks of isatuximab?
Benefits
In the phase III study the primary endpoint of progression free survival showed better outcome for patients treated with the isatuximab regimen compared with patients treated with the comparator regimen.

Risks
The company identified numerous adverse events of special interest including infusion related reactions, neutropenia and associated complications, thrombocytopenia, infections, tumour lysis syndrome, haemolytic disorders and blood cell transfusion and second primary malignancies. Such adverse events were more common and tended to be more severe in the current product arm of the phase III study. The nature and extent of adverse events is not unexpected for this type of medicinal product.
Neutralising antibodies were not detected in the pivotal study.

Why has isatuximab been given a positive Early Access to Medicine Scientific opinion?
Multiple myeloma (MM) is a malignant plasma cell disease that is characterised by clonal proliferation of plasma cells in the bone marrow (BM) and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]). Relapsed / refractory multiple myeloma is a life-threatening and seriously debilitating condition.

Although MM treatment has improved remarkably over the last two decades with the introduction of autologous stem cell transplantation and the introduction of numerous novel agents, once a patient becomes refractory to those agents, survival is limited, and MM remains an incurable disease in the vast majority of patients.

Isatuximab has been shown to significantly improve progression free survival and also to significantly improve overall response rate with an adverse event profile that can be considered to be clinically manageable.

The prospect of improved overall survival in the context of patients with advanced disease is considered to outweigh the burden of added weight of adverse events.

What are the uncertainties?
The overall survival data are not yet mature.
In addition, the efficacy of isatuximab in patients with primary refractory disease is unknown because these patients were excluded from the pivotal trial.

Are there on-going clinical studies?
There are several on-going clinical studies investigating the pharmacokinetics, pharmacodynamics, efficacy and safety of isatuximab in various drug combination regimens in patients with MM.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that isatuximab is used as safely as possible. Based on this plan, the Company that makes isatuximab must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including possible side effects and recommendations for preventing or minimising the impact of 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 isatuximab) through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the Company.

Healthcare professionals will receive a physician pack and training prior to commencement of patient treatment.

Patients in the EAMS will also receive an alert card from their doctor summarising the important risk with the medicine and the details of their treating oncologist. Patients should carry the card with them at all times in case they need treatment or advice from a healthcare professional that is not familiar with isatuximab treatment.

Other information about isatuximab – see EAMS Treatment Protocol