Early Access to Medicines Scientific Opinion - Public Assessment Report
Alecensa
Alectinib as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
Roche Products Limited

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 (as allowed under EU legislation). The General Medical Council's prescribing guidance: Prescribing unlicensed medicines can be found here: http://www.gmc-uk.org/mobile/news/14327

The 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 neither be regarded as either a licensed indication or a future commitment by the MHRA to licence such a medicine.

Alectinib

What is alectinib?

Alectinib is an anti-neoplastic agent. It is a tyrosine kinase inhibitor (TKI) that targets ALK and RET.

What is alectinib used to treat?

Alectinib is used to treat adult patients with advanced ALK- positive non-small cell lung cancer who have not previously received treatment for their advanced disease.

How is alectinib used?

Alectinib treatment should be started and supervised by a doctor experienced in the use of anticancer medicinal products. Tumour tissue must be tested using a validated ALK assay and found to be ALK-positive before starting treatment with alectinib. Alectinib is taken orally at the recommended dose of 600mg (four 150mg capsules) twice daily with food (total daily dose 1200mg). Treatment with alectinib should be continued until disease progression or unacceptable toxicity. Management of adverse events may require dose reduction, temporary interruption or discontinuation of alectinib treatment.
No dose adjustment is required in patients with renal impairment or mild hepatic impairment. Alectinib is not recommended in patients with moderate or severe hepatic impairment.

How does alectinib work?

Alectinib has been shown in pre-clinical studies to inhibit the activity of ALK tyrosine kinase, leading to blockage of downstream signalling pathways, including STAT 3 and PI3K/AKT, that are involved in tumour cell proliferation and survival. Alectinib promotes cancer cell death by restoring apoptosis and inhibiting tumour cell growth and proliferation.

How has alectinib been studied?

The main study was a global Phase III open – label clinical trial (BO28984, ALEX) involving 303 patients with advanced ALK-positive NSCLC who had not previously received an ALK-inhibitor or been treated for their advanced disease; 152 patients were randomized to receive alectinib 600mg twice daily and 151 patients were randomized to receive crizotinib 250mg twice daily.

Alectinib was also studied in another Phase III trial (JO28928, J-ALEX) in ALK-inhibitor naïve patients in Japan. J-ALEX compared a lower dose of alectinib (300mg twice daily, the approved dose in Japan) to crizotinib 250mg twice daily. A total of 103 patients were randomized in the alectinib arm and 104 patients in the crizotinib arm.
A first in human Phase I/II study in Japan (AF-001JP) investigated various doses of alectinib in 70 patients with advanced ALK-positive NSCLC who had received previous chemotherapy treatment.

What are the benefits and risks of alectinib?
Benefits
In both the J-ALEX and ALEX studies, alectinib prolonged progression free survival (PFS) assessed by an independent review committee (IRC) in comparison to crizotinib. In both studies the PFS with crizotinib was around 10-11 months. In ALEX, alectinib improved the IRC assessed PFS by 15.3 months (hazard ratio =0.50). Alectinib also prolonged the time until progression of brain metastases; at 1 year 41.4% of patients treated with crizotinib had CNS progression compared to 9.4% treated with alectinib.

Risks
In the ALEX study the safety profile for alectinib was comparable, or in some aspects favourable, relative to crizotinib. The overall incidence of adverse events was slightly lower in the alectinib arm There was a lower incidence of GI toxicity, CNS toxicity and eye disorders in the alectinib arm. Some adverse events (AEs) occurred at a higher rate in the alectinib arm: increased blood bilirubin (1% crizotinib vs.15% alectinib), increased weight (0% vs. 10%), myalgia (2% vs. 16%), musculoskeletal pain (2% vs. 7%), anaemia (5% vs. 20%) and photosensitivity reaction (0% vs. 5%). The Grade ≥3 AEs which occurred at a higher frequency (≥2%) in the alectinib arm were increased blood bilirubin, anaemia, lung infection and acute kidney injury.

Why has alectinib been given a positive Early Access to Medicine Scientific opinion?
PIM designation
The Applicant received a PIM designation for alectinib on 12 April 2017 for the proposed indication.

Life-threatening or seriously debilitating condition
Advanced/metastatic lung cancer is a life threatening and seriously debilitating condition with a high morbidity and mortality. It is the most common cause of cancer death in the UK. Translocations involving the ALK tyrosine kinase are present in approximately 4% of NSCLC adenocarcinoma and occur more frequently in non-smokers and younger patients. The lifetime incidence of brain metastases in the ALK-positive patients may be as high as 50%.

High unmet need
At the time of the PIM designation, crizotinib was the only ALK inhibitor approved in the EU for treatment of previously untreated NSCLC patients harbouring an ALK rearrangement. Limitations of crizotinib include the development of resistance and consequent relapse and suboptimal control of intracranial metastases. Also, crizotinib is known to be associated with significant toxicities.
Since the PIM designation meeting, the CHMP (May 2017) recommended extension of the ceritinib indication to include first-line treatment of adult patients with ALK-positive advanced NSCLC. Ceritinib has been shown to have a superior PFS to platinum-based chemotherapy but the benefit was less marked in patients with CNS metastases at baseline compared to the full trial population. Tolerability is an issue for ceritinib with a high proportion of patients requiring dose reduction or treatment interruption. Therefore, it is considered that an unmet medical need remains in the population requiring first line treatment of ALK-positive NSCLC.

Major advantage over methods currently used in the UK
Evidence to support the designation was provided from non-clinical and clinical data. Pre-clinically there was evidence of strong growth inhibitory activity in cell based assays, including in ALK mutations associated with crizotinib resistance, and good CNS penetration in intra-cranially implanted tumour mouse models.
Pre-planned interim analysis data was presented from a Phase III Japanese study (J-ALEX) and top-line data from the Phase III global study (ALEX). These showed improved PFS compared to crizotinib in ALK-inhibitor naïve patients. Central nervous system efficacy was observed with alectinib and the benefit in the subgroup of patients with CNS metastases at baseline was consistent with that of the full population treated with alectinib. Therefore, alectinib is likely to offer a major advantage over the current first -line treatments of ALK-positive advanced NSCLC used in the UK.

Positive benefit risk balance
From the clinical studies to date, it can be concluded that alectinib offers a potential for improved efficacy outcomes in the first line setting. It is noted that the alectinib dose studied in J-ALEX is half the dose that would be utilised in the UK (300mg bd vs. 600mg bd) due to cessation of dose escalation in the Japanese population rather than observed PK differences. Therefore, the safety data from J-ALEX cannot be used directly to suggest a more favourable safety and tolerability profile for alectinib compared with crizotinib. However, as alectinib has been licensed for second line treatment of ALK-positive advanced lung cancer based on Phase 1/2 studies conducted with the planned UK dose, the safety profile of alectinib has been assessed as acceptable. In addition, the top-line data from the ALEX study indicates that the safety profile of alectinib is at least comparable to crizotinib.

What are the uncertainties?
Initial top line data from the ALEX study have been presented but a detailed analysis has not been provided and overall survival results for alectinib in comparison to crizotinib are not yet available. Alectinib has been directly compared to the ALK-inhibitor crizotinib but not to the other ALK inhibitor approved for first-line monotherapy treatment of adult patients with ALK-positive advanced NSCLC (ceritinib)

Are there on-going clinical studies?
The ALEX study is ongoing.

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

Healthcare professionals will be asked by the company to report adverse effects experienced by patients receiving alectinib through the scheme. 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 also receive an alert card from their doctor summarising the important risks 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 who is not familiar with alectinib treatment.

Other information about alectinib
See EAMS Treatment Protocol