Part VI: Summary of the RMP

Summary of RMP for Alunbrig (brigatinib)

This is a summary of the RMP for Alunbrig. The RMP details important risks of Alunbrig, how these risks can be minimized, and how more information will be obtained about Alunbrig's risks and uncertainties (missing information).

Alunbrig's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to HCPs and patients on how Alunbrig should be used.

This summary of the RMP for Alunbrig should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Alunbrig's RMP.

I. The Medicine and What It Is Used For

Alunbrig is authorized for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib (see SmPC for the full indication). It contains brigatinib as the active substance and it is given by mouth.

Further information about the evaluation of Alunbrig's benefits can be found in Alunbrig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/alunbrig

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Alunbrig, together with measures to minimize such risks and the proposed studies for learning more about Alunbrig's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs.
- Important advice on the medicine's packaging.
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Alunbrig, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Alunbrig is not yet available, it is listed under ‘missing information’ below.

II.A List of Important Risks and Missing Information

Important risks of Alunbrig are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alunbrig. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	• Pulmonary toxicity (including EOPEs and later-onset pneumonitis). • Hypertension. • Bradycardia. • DDI with strong CYP3A inhibitors and strong and moderate CYP3A inducers.
Important potential risks	• Hepatotoxicity. • Myopathy, including rhabdomyolysis and cardiomyopathy. • Pancreatitis. • Retinal degeneration, macular degeneration. • Embryofetal and developmental toxicity.
Missing information	• Effects on male and/or female fertility. • Long-term safety. • DDI with CYP3A4 substrates.

II.B Summary of Important Risks

Important Identified Risk: Pulmonary Toxicity (including EOPE and later-onset pneumonitis)	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Increasing age (>60 years) and shorter interval between last dose of crizotinib and first dose of brigatinib (<7-day interval) are considered to be specific risk factors for pulmonary events.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (ILD/pneumonitis) 4.4 Special warnings and precautions for use (Pulmonary adverse reactions) 4.8 Undesirable effects (Pulmonary adverse reactions) **Additional risk minimization measures:** PAC
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Brigatinib PASS

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Risk factors for hypertension per se include: age, ethnicity, family history of hypertension and genetic factors, lower education and socioeconomic status, greater weight, lower physical activity, tobacco use, psychosocial stressors, sleep apnea, and dietary factors (including dietary fats, higher sodium intake, lower potassium intake, and excessive alcohol intake). However, no specific risk factors for brigatinib-induced hypertension have been identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Identified Risk: Bradycardia	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Several available ALK inhibitors produce bradycardia. Risk factors for bradycardia per se include: increased age, hypothyroidism, concomitant medications (eg, drugs for the treatment of hypertension, Alzheimer's disease, heart disease, heart failure and arrhythmias), exposure to certain toxins, cardiac disease, electrolyte imbalances, sleep apnea, systemic lupus erythematosus or other collagen vascular diseases (rare), head injuries, hypothermia, hypoglycemia and infectious diseases (eg, diphtheria, rheumatic fever, viral myocarditis, Lyme disease, and Chagas disease). Specific risk factors for brigatinib-induced bradycardia are not known. However, data pertaining to crizotinib may provide useful insights as to potential risk factors based up a class effect. A large-scale retrospective analysis of 1053 patients with ALK+ NSCLC treated with crizotinib, Ou et al showed that a pretreatment heart rate of <70 beats per minute was the strongest predictor of the development of sinus bradycardia by logistic regression analysis, with an observed 5-fold increase in the likelihood of developing sinus bradycardia during crizotinib treatment compared with patients with a pretreatment heart rate of ≥70 beats per minute. An ECOG score of 0 or 1 was marginally associated with the development of sinus bradycardia during crizotinib treatment.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Identified Risk: DDI With Strong CYP3A Inhibitors and Strong and Moderate CYP3A Inducers	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is sufficient evidence demonstrating causal association.
Risk factors and risk groups	Patients at risk are patients coadministered brigatinib and other drugs which are strong CYP3A inhibitors and strong and moderate CYP3A inducers.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.4 Special warnings and precautions for use (DDIs) 4.5 Interaction with other medicinal products and other forms of interaction (CYP3A inhibitors; CYP3A inducers)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is evidence to suspect the possibility of a causal relationship between these events and brigatinib.
Risk factors and risk groups	Patients with underlying liver impairment or other comorbid conditions, patients taking other medications which may affect

	liver function or which may affect the concentrations of brigatinib.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (elevation of hepatic enzymes) 4.4 Special warnings and precautions for use (elevations of hepatic enzymes) 4.8 Undesirable effects (elevation of hepatic enzymes)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Potential Risk: Myopathy, Including Rhabdomyolysis and Cardiomyopathy	
Evidence for linking the risk to the medicine	On the basis of the incidence of CPK elevation observed in clinical study results, there is a possibility of a causal relationship between these events and brigatinib. CPK elevation can be indicative of possible myopathy, including rhabdomyolysis and cardiomyopathy.
Risk factors and risk groups	Risk factors for raised CPK per se include concomitant use of drugs capable of inducing myopathies such as cholesterol-lowering agents, HIV medications, antifungal and immunosuppressants. High CPK levels may be seen in people who have brain injury or stroke, convulsions, delirium tremens, dermatomyositis or polymyositis, electric shock, heart attack, myocarditis, pulmonary infarction, muscular dystrophies, myopathy, and rhabdomyolysis. No specific risk factors have been identified for brigatinib-induced blood CPK elevation.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use (CPK elevation) 4.8 Undesirable effects
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is evidence to suspect the possibility of a causal relationship.
Risk factors and risk groups	Risk factors for pancreatic enzyme elevation per se include cholecystitis, kidney failure, gallstones- or alcohol-induced pancreatitis, and drug-induced pancreatitis. No specific risk factors for brigatinib-induced pancreatic enzyme elevation have been identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (elevation of lipase or amylase) 4.4 Special warnings and precautions for use (elevations of Pancreatic enzymes) 4.8 Undesirable effects (elevations of pancreatic enzymes)

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Potential Risk: Retinal Degeneration, Macular Degeneration	
Evidence for linking the risk to the medicine	Vision impairment is a class effect observed with ALK TKIs. On the basis of clinical study results, there is evidence to suspect the possibility of retinal and macular degeneration.
Risk factors and risk groups	Risk factors for visual impairment per se include age and the associated comorbidities like AMD, glaucoma, cataract and diabetic retinopathy. Risk factors for AMD include family history of AMD and CV risk factors such as hypertension and cigarette smoking. No specific risk factors for brigatinib-associated visual impairment have been identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (visual disturbance) 4.4 Special warnings and precautions for use (visual disturbance) 4.8 Undesirable effects (visual disturbance)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Potential Risk: Embryofetal and Developmental Toxicity	
Evidence for linking the risk to the medicine	On the basis of nonclinical study results there is evidence to suspect potential embryofoetal and developmental toxicity.
Risk factors and risk groups	Sexually active women of childbearing potential and male patients who are sexually active with women of childbearing potential.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing Information: Effects on Male and/or Female Fertility	
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing Information: Long-term Safety	
Risk minimization measures	**No risk minimization measures**
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing Information: DDI with CYP3A4 Substrates	
Risk minimization measures	**Routine risk minimization measures:** SmPC Section: 4.5 Interaction with other medicinal products and other forms of interaction
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the MA

AP26113-13-301

Purpose of the study: to further characterise the efficacy and safety of brigatinib in the treatment of patients with ALK-positive NSCLC

II.C.2. Other Studies in Postauthorization Development Plan

Brigatinib PASS

Purpose of the study:

- To describe the occurrence and outcome of EOPE in patients with ALK+ NSCLC receiving brigatinib or other TKIs.
- To assess the receipt and use of the PAC in patients treated with brigatinib