Summary of risk management plan for CAPRELSA (Vandetanib)

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

CAPRELSA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CAPRELSA should be used.

This summary of the RMP for CAPRELSA 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 CAPRELSA's RMP.

1. THE MEDICINE AND WHAT IT IS USED FOR

CAPRELSA is authorized for medullary thyroid cancer (MTC) that cannot be removed by surgery or has spread to other parts of the body. It contains vandetanib as the active substance and it is given by oral route. CAPRELSA works by slowing down the growth of new blood vessels in tumors (cancers). This cuts off the supply of food and oxygen to the tumor. CAPRELSA may also act directly on cancer cells to kill them or slow down their growth.

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002315/human_med_001529.jsp&mid=WC0b01ac058001d124

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of CAPRELSA, together with measures to minimise such risks and the proposed studies for learning more about CAPRELSA's risks, are outlined in the next sections.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- 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 CAPRELSA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) 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 CAPRELSA is not yet available, it is listed under 'missing information' outlined in the next section.

2.1. List of important risks and missing information

Important risks of CAPRELSA 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 CAPRELSA. 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).

Table 1 - List of important risks and missing information

Important identified risks	Posterior reversible encephalopathy syndrome (also known as Reversible posterior leukoencephalopathy syndrome) QTc prolongation and Torsades de pointes
Important potential risks	Teeth and bone abnormalities in the paediatric population Medication errors related to paediatric population
Missing information	None

2.2. Summary of important risks

Table 2 - Important identified risk: Posterior reversible encephalopathy syndrome (also known as Reversible posterior leukoencephalopathy syndrome) with corresponding risk minimization activities and additional pharmacovigilance activities

Posterior reversible encephalopathy syndrome (also known as Reversible posterior leukoencephalopathy syndrome)	
Evidence for linking the risk to the medicine	Clinical trials, literature and postmarketing experience.
Risk factors and risk groups.	Hypertensive encephalopathy, pre-eclampsia/eclampsia, renal failure, and cytotoxic or immunosuppressant agents, including VEGF antagonists, have been implicated in the pathogenesis of PRES. *a, b*
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in section 4.4 (brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status) **Additional risk minimization measures:** Educational materials for HCP and Patient alert card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None (Yearly survey to CAPRELSA prescribers and potential prescribers to assess effectiveness of educational materials final report enclosed with RMP v13.0 submission dossier; The results indicate that the educational materials were distributed to a large percentage of health care providers in each of the selected European markets. The educational materials have been effective in informing HCPs as to the risk of CAPRELSA. Based on the level of the data/responses captured and given the high level of knowledge and understanding of the physicians, the data showed consistency or improvement over the 3-year period).

HCP: Healthcare Professional; MRI: Magnetic Resonance Imaging; PRES: Posterior Reversible Encephalopathy; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; VEGF: Vascular Endothelial Growth Factor.

a Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015 Sep;14(9):914-925.

b Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. J Neuroimaging. 2004;14:89.

Table 3 - Important identified risk: QTc prolongation and Torsades de pointes with corresponding risk minimization activities and additional pharmacovigilance activities

QTc prolongation and Torsades de pointes	
Evidence for linking the risk to the medicine	Clinical studies, literature and postmarketing experience.
Risk factors and risk groups.	QTc prolongation increases the risk for developing Torsades de pointes. Patients with a QTc interval of greater than 500 msec are at greater risk. Risk factors that have been linked to QTc prolongation in cancer patients include: female sex, old age, pre-existing heart disease, renal or hepatic dysfunction resulting in drug toxicity, electrolyte imbalances as a result of severe nausea, vomiting, diarrhoea, and decreased oral intake, and concomitant medications such as 5-HT3 antagonists. However, while many medications may prolong the QTc interval, few have been clearly associated with Torsades de pointes.

QTc prolongation and Torsades de pointes	
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in section 4.4 (an ECG and levels of serum potassium, calcium and magnesium and TSH should be obtained at baseline at 1, 3, 6 and 12 weeks after starting treatment and every three months for at least a year thereafter) **Additional risk minimization measures:** Educational materials for HCP and Patient alert card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study D4200C00104 (OBS14778)

5-HT: 5-Hydroxytryptamine; ECG: Electrocardiogram; HCP: Healthcare Professional; SmPC: Summary of Product Characteristics; TSH: Thyroid Stimulating Hormone.

Table 4 - Important potential risk: Teeth and bone abnormalities in the paediatric population with corresponding risk minimization activities and additional pharmacovigilance activities

Teeth and bone abnormalities in the paediatric population	
Evidence for linking the risk to the medicine	**Non-clinical studies:** Repeat dose toxicity studies (rat and dog) and reproductive and development studies in the rat. **Clinical studies:** Phase I/II trial in children and adolescents with hereditary medullary thyroid cancer (IRUZACT0098). Tyrosine kinase inhibitor have been associated with elevated TSH as a drug class effect. [a] It is well recognized that thyroid hormone is necessary for normal growth and in children with hypothyroidism growth is slowed. In this phase I/II (IRUSZACT0098) study, 13 patients were analyzed for the patterns of TSH levels. Eleven patients had undergone a total thyroidectomy and were athyreotic requiring thyroxine replacement. All of these 11 patients received therapy with vandetanib for >6 months, and while on vandetanib therapy these patients exhibited significantly increased TSH levels. [a] Doses of thyroxine replacement were increased an average of 36.6% in order to achieve correction of the TSH levels.) Additionally, over the duration of the ongoing study, the investigators continued to monitor and adjust the thyroxine dosing individualized to each patient as dosages of TKIs were altered, and patients grew and and progressed through puberty. [a] In summary, vandetanib has been found that it can affect thyroid function leading to an increase in thyroxine requirement. However, in the phase I/II study done at the NIH these issues were monitored and it was found that vandetanib did not impair linear growth. [b]
Risk factors and risk groups.	Paediatric patients (ages 5-18, inclusive) being administered the product by a parent or caregiver. Vandetanib which functions as an inhibitor of VEGF receptor has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in nonclincial studies only. Follow-up from NIH revealed a subset of patients followed between 5-9 years which revealed no overt growth or bone/teeth disorders. Vandetanib has been found that it can affect thyroid function leading to an increase in thyroxine requirement that should be considered as a risk factor. However, in the phase I/II study done at the NIH these issues were monitored and it was found that vandetanib did not impair linear growth. [b] Childhood cancer patients may have impaired growth before, during or after successful treatment for their cancer. A number of factors are responsible for this, including the disease process itself, complications of treatment (infection), direct effects during treatment

Teeth and bone abnormalities in the paediatric population	
	(anorexia, vomiting) and direct and ind irect late effects attributable to therapy. The following risk factors can be identified: Cranial radiotherapy can cause growth hormone deficiency and growth retardation, which in turn may be compounded by other pituitary hormone deficiencies, particularly adrenocorticotrophin, follicle stimulating hormone, luteinising hormone and thyroid stimulating hormone. Localised tumor treatments may affect growth and function of individual organs. For example, spinal growth is adversely affected by spinal irradiation and may result in skeletal disproportion. Abdominal surgery and/or radiotherapy may cause sex hormone deficiencies and secondary effects on growth and pubertal development. Chemotherapy alone may also have significant effects on growth. The particular risks of growth impairment for any individual survivor depend upon the cancer type, the treatment given and the age at presentation. [c]
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in section 5.3. **Additional risk minimization measures:** Educational materials for HCPs.

HCP: Healthcare Professional; NIH: National Institute of Health; SmPC: Summary of Product Characteristics; TKI: Tyrosine Kinase Inhibitor; TSH: Thyroid Stimulating Hormone; VEGF: Vascular Endothelial Growth Factor.

a Lodish M, Gkourogianni A, Bornstein E, Sinaii N, Fox E, Chuk M, et al. Patterns of thyroid hormone levels in pediatric medullary thyroid carcinoma patients on vandetanib therapy.Int J Pediatr Endocrinol. 2015;2015(1):3.

b Fox E, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO, et al. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. Clin Cancer Res. 2013 Aug 1;19(15):4239-48.

c Scottish Intercollegiate Guidelines Network. Long term follow-up of survivors of childhood cancer. A national clinical guideline. March 2013.

Table 5 - Important potential risk: Medication errors related to paediatric population with corresponding risk minimization activities and additional pharmacovigilance activities

Medication errors related to paediatric population	
Evidence for linking the risk to the medicine	One paediatric case of medication error has been reported to date. There is no evidence that medication errors are a risk in the paediatric population. However, the different posology in paediatric patients makes medication errors a potential risk.
Risk factors and risk groups.	Paediatric population, being administered the product by a parent or caregiver.
Risk minimization measures	**Routine risk minimization measures:** Dose adjustments in paediatric patients with MTC mentioned in SmPC section 4.2. **Additional risk minimization measures:** Educational materials for HCPs and dosing and monitoring guide for patients and patient's caregivers

HCP: Healthcare Professional; MTC: Medullary Thyroid Cancer; SmPC: Summary of Product Characteristics.

2.3. Post-authorization development plan

2.3.1. Studies which are conditions of the marketing authorization

The following study is condition of the marketing authorization:

Table 6 - Studies which are conditions of the marketing authorization

Study D4200C00104 (OBS14778) **This is a multinational, multicenter, non-interventional (observational), prospective and retrospective study. European countries where vandetanib is on the market will participate in the study.** **This study is being conducted to fulfil the specific obligation post-authorisation measure for the conditional marketing authorisation. It is carried on to confirm in real life conditions the benefit/risk of vandetanib (CAPRELSA) 300 mg, both in RET negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. The clinical benefit of vandetanib (CAPRELSA) 300 mg has previously been established in a clinical trial (Study D4200C00058) on the basis of a clinically and statistically significant advantage in PFS which was supported by a high response rate and substantial DOR.**
Purpose of the study This study is being conducted: • To fulfil the specific obligation post-authorization measure for the conditional marketing authorization: o "In order to confirm the efficacy and safety of CAPRELSA in RET-negative patients, the MAH should submit: - The clinical study report of study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (CAPRELSA) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumor samples from the pivotal study D4200C00058." • To confirm in real life conditions the benefit/risk of vandetanib (CAPRELSA) 300 mg, both in RET negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. • To determine the ORR, DCR, DOR and TTR for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation Negative. • To explore the clinical outcomes (including but not limited to PFS and ORR) amongst RET mutation negative patients not treated with vandetanib. • To compare PFS for patients treated with vandetanib who are RET mutation positive to patients treated with vandetanib who are RET mutation negative.

DCR: Disease Control Rate; DOR: Duration of Response; MTC: Medullary Thyroid Cancer; ORR: Objective Response Rate; PFS: Progression-Free Survival; RET: Rearranged During Transfection; TTR: Time to Response.

2.3.2. Other studies in post-authorization development plan

None