Summary of the Risk Management Plan (RMP) for CAPRELSA®

CAPRELSA® (Vandatanib)
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of CAPRELSA® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of CAPRELSA® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of CAPRELSA®.

I.THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) with RET mutation (RET: rearranged during transfection) in adults with unresectable, locally advanced or metastatic disease.

According to EU SmPC

CAPRELSA is authorized for the treatment of aggressive and symptomatic rearranged during transfection (RET) mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. CAPRELSA is indicated in adults, children and adolescents aged 5 years and older. 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.

II.RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of CAPRELSA, together with measures to minimize such 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 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 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.

II.A 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 21 - 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 pediatric population Medication errors related to pediatric population
Missing information	None

QTc: Corrected QT Interval.

II.B Summary of important risks

Table 22 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities if any: Posterior reversible encephalopathy syndrome (also known as Reversible posterior leukoencephalopathy syndrome)

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. (54)(60)
Risk minimization measures	**Routine risk minimization measures:** • Labeled in SmPC section 4.8. • Labeled in PL section 4. • Brain MRI test advised in SmPC 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.

HCP: Healthcare Professional; MRI: Magnetic Resonance Imaging; PL: Patient Leaflet; PRES: Posterior Reversible Encephalopathy; SmPC: Summary of Product Characteristics; VEGF: Vascular Endothelial Growth Factor.

Table 23 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities if any: QTc prolongation and Torsades de pointes

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.	Corrected QT interval 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, diarrhea, 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.
Risk minimization measures	**Routine risk minimization measures:** • Labeled in SmPC sections 4.2, 4.3, 4.5, 4.8 and 4.9. • Labeled in PL sections 2 and 4. • Electrocardiogram and blood tests advised in SmPC 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.

5-HT: 5-Hydroxytryptamine; ECG: Electrocardiogram; HCP: Healthcare Professional; QTc: Corrected QT Interval; PL: Patient Leaflet; SmPC: Summary of Product Characteristics; TSH: Thyroid Stimulating Hormone.

Table 24 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities if any: Teeth and bone abnormalities in the pediatric population

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 MTC (IRUZACT0098). Tyrosine kinase inhibitors have been associated with elevated TSH as a drug class effect. (75) 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. (75) Doses of thyroxine replacement were increased an average of 36.6% in order to achieve correction of the TSH levels. (75) 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 progressed through puberty. (75) 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. (76)

Risk factors and risk groups.	Pediatric patients (ages 5-18, inclusive) being administered the product by a parent or caregiver. Vandetanib which functions as an inhibitor of VEGFR has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in non-clinical 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. (76) 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 (anorexia, vomiting) and direct and indirect 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, luteinizing hormone and TSH. Localized 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. (79)
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC section 5.3.

Teeth and bone abnormalities in the paediatric population	
	Additional risk minimization measures: Educational materials for HCPs.

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

Table 25 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities if any: Medication errors related to pediatric population

Medication errors related to pediatric population	
Evidence for linking the risk to the medicine	Postmarketing data.

Risk factors and risk groups.	Pediatric population, being administered the product by a parent or caregiver.
Risk minimization measures	**Routine risk minimization measures:** • Labeled in SmPC section 4.2. • Labeled in PL section 3. **Additional risk minimization measures:** Educational materials for HCPs and dosing and monitoring guide for patients and patient's caregivers.

HCP: Healthcare Professional; PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

VI II.C Post-authorization development plan

II.C.I *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of CAPRELSA.

II.C.II *Other studies in post-authorization development plan*

There are no studies required for CAPRELSA.