15 September 2022
EMA/CHMP/113263/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Caprelsa

International non-proprietary name: vandetanib

Procedure No. EMEA/H/C/002315/R/0055

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	15 Aug 2022	15 Aug 2022	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	06 Sep 2022	06 Sep 2022	☐
☐	CHMP and PRAC members comments	08 Sep 2022	n/a	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	09 Sep 2022	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	13 Sep 2022	15 Sep 2022	☐
☒	Opinion	15 Sep 2022	15 Sep 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: interim results/outcome of the SOB that is a non-interventional PASS study challenging the benefit/risk balance of the product; new imposed non-interventional PASS resulting from the annual renewal (annex II condition); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the PRAC rapporteur.

Criteria for CHMP plenary discussion: interim results/outcome of the SOB challenging the benefit/risk balance of the product; fulfilment of all SOBs; non-compliance with SOB(s); new imposed PASS/PAES resulting from the annual renewal (annex II condition or new SOB); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the CHMP rapporteur.

[3] Sections related to data on non-interventional PASS imposed as an SOB, Risk Management Plan (safety concerns, Pharmacovigilance plans, Risk minimisation Measures), sections on issues originating from parallel/recent PSUR or signal assessment, additional monitoring, pharmacovigilance inspections and preliminary conclusions on the benefit/risk balance.

Procedure resources	
CHMP Rapporteur:	Alexandre Moreau

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1. Background information on the annual renewal

The European Commission issued on 17 February 2012, a conditional marketing authorisation (MA) for Caprelsa This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Genzyme Europe BV, submitted to the Agency on 28 July 2022 an application for renewal of the conditional MA for Caprelsa. The expiry date of the MA is 21 February 2023.

The period covered by this annual renewal is 20-May-2021 to 19-May-2022.

Reference is made to the ongoing procedure **EMEA/H/C/002315/II/0043** which intends to fulfil the Specific Obligation and to switch the conditional marketing authorisation into a marketing authorisation not subject to specific obligations.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations (SOBs)

This being a conditional Marketing Authorisation and pursuant to Article 14a(4) of Regulation (EC) No726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
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 thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058.	Ongoing-due date March 2021

On 04 March 2020, the MAH submitted a type II variation for Caprelsa(vandetanib) to request the closure of the Specific Obligation (SOB001), and consequently the switch from a conditional to a standard marketing authorisation (not subject to Specific Obligations). This variation (**EMEA/H/C/002315/II/0043)** is currently under review. A CHMP opinion is expected in September 2022.

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOB have been submitted that are assessed within the ongoing procedure **EMEA/H/C/002315/II/0043**.

2.2. Benefit-risk Balance

During the period covered by this annual renewal, no new data have emerged. Assessment of the data submitted in fulfilment of the SOB is provided in parallel in the procedure **EMEA/H/C/002315/II/0043**. As reference the evaluation of the data indicate no change in the benefit/risk of the product which remains positive and acceptable considering the restricted therapeutic indication of Caprelsa (vandetanib) to RET mutant medullary thyroid cancer (MTC).

3. Recommendations

Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations as per parallel variation (**EMEA/H/C/002315/II/0043**) and having confirmed that benefit risk balance for Caprelsa remains favourable in the therapeutic indication restricted to RET mutant medullary thyroid cancer (MTC) as per the pending outcome of the procedure **EMEA/H/C/002315/II/0043,** therefore recommends by consensus the renewal of the conditional marketing authorisation.

Amendments to the marketing authorisation

The renewal requires no amendments to the terms of the marketing authorisation.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- ***Additional risk minimisation measures***

Prior to launch of CAPRELSA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.
The MAH shall ensure that in each Member State where CAPRELSA is marketed, all healthcare professionals (HCPs) and patients / caregivers who are expected to prescribe, dispense and use CAPRELSA have access to/are provided with an **educational package** containing:

HCPs

- The summary of Product Characteristics (SmPC);
- The educational material, including:
    - Information about the risks associated with CAPRELSA:
        - QTc prolongation and Torsades de pointes
        - Posterior reversible encephalopathy syndrome (PRES);
        - Teeth and bone development abnormalities in pediatric patients

        - Medication errors in the pediatric population
    - The Physicians' dosing and monitoring guide for paediatric patients;
- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

Patients / caregivers

- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

The **HCPs educational materials** should include the following key elements:

QTc prolongation and Torsades de pointes

- CAPRELSA prolongs the QTc interval and can cause Torsades de pointes and sudden death
- CAPRELSA treatment must not be started in patients:
    - Whose ECG QTc interval is greater than 480 msec;
    - Who have congenital long QTc syndrome;
    - Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades de pointes have been corrected;
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed;
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking CAPRELSA. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made;
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought;
- Details of medicinal products where the co-administration of CAPRELSA is either contraindicated or not recommended;
- The role and use of the Patient Alert Card.

Posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leukoencephalopathy syndrome (RPLS)

- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. A brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status;
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take;

- The role and use of the Patient Alert Card.

Teeth and bone development abnormalities in pediatric patients

- Vandetanib was found not to impair linear growth in clinical trials conducted in children and adolescents;
- Vandetanib has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in non-clinical studies;
- The need to closely monitor teeth and bone abnormalities in the paediatric population;

Medication errors in the paediatric population

The **Physicians' dosing and monitoring guide for paediatric patients** should contain the following key elements:

- How CAPRELSA dose for infants and adolescents is calculated;
- The posology regimens according to patient's body surface area (BSA), including a visual representation of the two-week posology regimen per BSA;
- How CAPRELSA is used / administered;
- Instructions on how to use the dosing and monitoring guide and the daily tracker for paediatric patients and caregivers.

The **dosing and monitoring guide for patients and patient's caregivers** should contain the following key elements:

- What CAPRELSA is, what it treats, how it is administered;
- How CAPRELSA dose is calculated;
- What are the side effects associated with CAPRELSA and which monitoring is requested;
- How to use the daily tracker table (including examples of a completed daily tracker);
- The general daily tracker for 14 days and blank copies of the daily tracker.

The **Patient Alert Card** should include the following key elements:

- Information about the risks of QTc prolongation and Torsades de pointes, and Posterior reversible encephalopathy syndrome (PRES);
- Signs or symptoms of the safety concerns and when to seek attention from a HCP;
- Not to stop taking CAPRELSA, or change the dose, without consulting the prescriber;
- Contact details of the CAPRELSA prescriber

● *Specific obligations to complete post-authorisation measures for the conditional marketing authorisation*

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
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 thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study **D4200C00058**.	March 2021

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☐	☒
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☒
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☒

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Table 1. Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB 001	An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU.	SOB 001 has been modified to ensure that comprehensive data are generated by the agreed due date (refer to section 5.2).

5.2. Outstanding Specific Obligations – status report for period covered

SOB 001:

Number	Description	Status
SOB 001	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 thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study **D4200C00058.**	Ongoing – due date March 2021

Reference is made to the ongoing procedure **EMEA/H/C/002315/II/0043** which intends to fulfil the Specific Obligation and to switch the conditional marketing authorisation into a marketing authorisation not subject to specific obligations.

5.3. Overall conclusion on Specific Obligations

Pending the outcome of the procedure **EMEA/H/C/002315/II/0043.**

6. Additional scientific data provided relevant for the assessment of the benefit/risk balance

6.1. EFFICACY

During the reporting period of this ACO, an addendum to the CSR of the pivotal study D4200C00058 (dated 10 March 2022) has been prepared which integrates a reanalysis of RET status using new methodologies. An amendment to the non-interventional study OBS14778 has also been performed. Efficacy and safety results are provided below.

► Addendum to CSR of Study D4200C00058 (LPS14811) "An International, Phase III, Randomized, Double Blinded, Placebo-controlled, Multi-center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer" (**Dated 10 March 2022**)

• In the original CSR of the Study, 79 patients had no M918T mutation identified. Of these 79 patients, 69 had enough tissue sample to allow a reanalysis of RET mutation status based on new available assays.

- Most patients were reclassified as RET mutant (52/69 patients) and a minority (17/69 patients) had no RET mutation (M918T or other) detected.

- Of these 17 RET negative patients, 14 patients had a RAS mutation (9 treated with vandetanib and 5 treated with placebo), 1 patient treated with vandetanib had a BRAF mutation and 2 patients (1 in each arm) had no mutation identified.

• In this addendum, newly identified RET mutant patients (n = 52) were pooled with RET mutant patients reported in the initial D4200C00058 CSR (n = 187), leading to a total number of 239 RET mutant patients and 17 RET negative patients. The efficacy end points included PFS based on central read RECIST assessment (primary end-point) as well as the following secondary end-points: ORR, DCR, OS, CEA and calcitonin serum responses.

• The efficacy of vandetanib, already established in RET mutant patients, was confirmed from this analysis including 52 additional RET mutant patients.

• Of those 17 patients RET negative, the activity of vandetanib remained numerically higher than placebo:

- The PFS HR was 0.21 (95% CI: 0.03 1.53) with a two-year PFS rate of 90% in patients treated with vandetanib versus 50% in patients treated with placebo.

- An objective tumor response was observed in 18.2% (2/11 RET negative patients; 2/9 (22.2%) RAS mutant patients) treated with vandetanib versus none of those treated with placebo (n = 6). Both patients with an objective response had a concomitant decline of CEA and/or calcitonin serum levels.

- The only RET negative patient who died from thyroid cancer received the placebo.

► Addendum to the PASS report OBS14778 (D4200C00104) "International Observational Study 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 Medullary Thyroid Cancer" **(09 March 2022)**

• Study OBS14778 (D4200C00104) was conducted to fulfill the post authorization specific obligation linked to the conditional MA of vandetanib. It was conducted to confirm, in real life conditions, the benefit/risk of vandetanib 300 mg, both in RET negative and RET mutant participants with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC.

• Because study OBS14778 was observational, the evaluation of objective response provided in the CSR was based on investigator assessment of imaging for all patients, including those coming from study D4200C00058. Since the primary analysis of study D4200C00058 was based on a blinded central review of imaging, the MAH thought it was more rigorous to reanalyze the objective response in study OBS14778 using the blinded central review dataset of study D4200C00058.

• Using this blinded central review data, 79 patients (instead of 75) were evaluable for analysis in study OBS14778, 58 RET mutant patients (instead of 55) and 21 RET negative patients (instead of 20).

- The objective response rate in RET negative patients remained lower than in RET mutant patients (9.5% vs 39.7%). Importantly, the two RET negative patients having an objective response were carrying a RAS mutation and came from the ZETA phase III study.

- The duration of treatment (27.6 months vs 23.4 months in RET negative vs RET mutant patients), the DCR (85.7% vs 87.9%) and PFS (35.7 months vs 25.4 months) were not influenced by RET status.

- Cancer death was lower in RET negative patients than in RET mutant patients (4.8% vs 13.8%).

• Treatment with vandetanib was associated with a decrease in calcitonin, which was delayed in RET negative versus RET mutant patients. There was also a decrease in CEA which was comparable in both RET negative and RET mutant patients.

CHMP rapporteur's comment:

Assessment of these data is part of the ongoing procedure **EMEA/H/C/002315/II/0043**.

Literature

Several publications on the activity of vandetanib were identified during the reporting period and are described hereafter. No new relevant efficacy and/or effectiveness findings in approved indications were identified during the reporting interval.

Romei C, Ramone T, Mulè C, Prete A, Cappagli V, Lorusso L et al. RET mutated C-cells proliferate more rapidly than non-mutated neoplastic cells. Endocr Connect. 2021 Feb;10(2):124-30 (6).

Background: A significantly higher prevalence of the RET p.Met918Thr somatic mutation, identified by direct sequencing, was previously reported in large MTC (> 2 cm) compared to smaller tumors. The aim

of this study was to correlate the full RET and RAS mutation profile, identified by a Next Generation Sequencing approach, with the growth rate, proliferation and tumor size of MTC.

Methods: Data of 149 sporadic MTC patients were correlated with RET mutations and Ki67 positivity. Eighty-one cases had a somatic RET mutation, 40 had a RAS mutation and 28 were negative.

Results: A significantly higher prevalence of RET mutations was found in MTC > 2 cm. A higher prevalence of RET more aggressive mutations, higher allelic frequencies and, higher percentage of Ki67 positive cells were found in larger tumors which had also a worse outcome. Our study highlights the predominant role of RET somatic mutations in MTC tumorigenesis. We demonstrate that RET mutation prevalence and allelic frequency (AF) are significantly higher in larger tumors.

Conclusions: Based on these results, we can conclude that RET mutated C-cells' growth and proliferation are more rapid than those of non-mutated cells and give origin to bigger and more aggressive MTC.

MAH comment: These results suggest that patients with RET mutant MTC have a worse prognosis compared to RAS mutant/RET negative and RAS negative/RET negative patients.

Brandenburg T, Tiedje V, Muchalla P, Theurer S, Weber F, Schmid KW, et al. Continued Discontinuation of TKI Treatment in Medullary Thyroid Carcinoma - Lessons from Individual Cases With Long-Term Follow-Up. Front Endocrinol (Lausanne). 2021 Sep 29;12:718418 (15).

Background: The aim of this retrospective analysis is to analyse impact of TKIs discontinuation on MTC disease course after longer-term therapy.

Methods: Medical records of 161 MTC patients with vandetanib treatment of up to 87 months followed by discontinuation for concerns of toxicity or due to side-effects in a tertiary referral endocrine tumour centre were retrospectively reviewed. Analysis included a review of patients' records for TKI indication, and treatment response as well indications for continued TKI discontinuation and follow-up by clinical assessment, calcitonin, and CEA doubling times as well as imaging (ultrasound, computed tomography [CT]).

Results: Seven MTC patients [six sporadic MTC, 1 Multiple Endocrine Neoplasia Type 2a (MEN2a)] with previous vandetanib treatment (median: 41 months; range 7-87 months) and continued TKI discontinuation were identified out of 161 analysed MTC files. TKI treatment was initiated due to high tumour burden and symptoms or RECIST progression in all patients.

• Two patients (29%) remained stable after discontinuation of vandetanib until now (follow-up of 47 and 61 months). Both patients had been on TKI therapy for 73 and 58 months.

• Five patients (71%) developed progressive disease after TKI discontinuation:

- In two patients, vandetanib was restarted after 45 and 52 months resulting again in disease control.

- One patient was enrolled in a new RET kinase inhibitor trial after 45 months of vandetanib discontinuation.

- Two patients declined restart of treatment due to mental health issues leading to discontinuation of vandetanib in the first place (after 7 and 38 months of treatment) and both patients died of rapidly progressive disease.

• At time points of tumour progression, calcitonin-doubling time (CDT) was < 2 years in all patients.

Conclusion: This case series suggests that discontinuation of long-term vandetanib treatment with documented stable disease does not automatically result in rapid disease progression but may be followed by prolonged "TKI free" stable disease in individual patients. Analysis of calcitonin and CDT

during discontinuation is indicated as it will unmask tumour progression earlier than imaging. Restart with the same TKI is possible in case of progression.

Parikh R, Hess LM, Esterberg E, Bhandari NR, Kaye JA. Diagnostic characteristics, treatment patterns, and clinical outcomes for patients with advanced/metastatic medullary thyroid cancer. Thyroid Res. 2022; 15(1):2 (16).

Background: Medullary thyroid cancer accounts for approximately 1.6% of new cases of thyroid cancer. The objective of this study was to describe patient characteristics, biomarker testing, treatment patterns, and clinical outcomes among patients with advanced/metastatic MTC in a real-world setting in the USA and to identify potential gaps in the care of these patients.

Methods: Selected oncologists retrospectively reviewed medical records of patients aged ≥ 12 years diagnosed with advanced MTC. Patients must have initiated ≥ 1 line of systemic treatment for advanced/metastatic MTC between January 2013-December 2018 to be eligible. Patient characteristics, biomarker testing, and treatment patterns were summarized descriptively; PFS and OS were estimated using the Kaplan-Meier method.

Results: The 203 patients included in this study had a mean (Standard Deviation [SD]) age of 52.2 (10.4) years; mean (SD) duration of follow-up from start of first-line treatment was 24.5 (16.0) months. Most patients (82.8%) were initially diagnosed with stage IVA, IVB, or IVC disease. Among all patients, 121 (59.6%) had testing for RET mutations, of whom 37.2% had RET-mutant MTC. The RET mutation type was reported for 28 patients; the most common mutations reported were M918T (64.3%) and C634R (32.1%). Of the 203 patients, 75.9% received only one line of systemic treatment for advanced disease, and 36% were still undergoing first-line therapy at the time of data extraction. Cabozantinib (30.0%), vandetanib (30.0%), sorafenib (17.2%), and lenvatinib (4.9%) were the most common first-line treatments. Among 49 patients who received second-line treatment, most received cabozantinib (22.4%), vandetanib (20.4%), lenvatinib (12.2%), or sunitinib (12.2%). Median PFS (95% CI) from start of first and second-line treatments was 26.6 months (20.8-60.8) and 15.3 months (6.6-not estimable [NE]), respectively. Median OS from initiation of first and second-line treatment was 63.8 months (46.3-NE) and 22.4 months (12.4-NE), respectively.

Conclusions: For the treatment of advanced/metastatic MTC, no specific preference of sequencing systemic agents was observed in the first and second-line settings. Considering the recent approval of selective RET inhibitors for patients with RET-mutant MTC, future research should investigate how treatment patterns evolve for these patients.

Buffet C, Leboulleux S, Kraeber-Bodéré F, Bodet-Milin C, Cabanes L, Dohan A, et al. Cardiac Metastasis from Medullary Thyroid Cancers with Long-Term Survival under Vandetanib. Eur Thyroid J. 2021 Nov;10(6):517-22 (17).

Background: Cardiac metastases from thyroid cancers are uncommon with a poor prognosis. There is a lack of long-term follow-up studies.

Cases: We report two cases of cardiac metastasis from MTC. Both patients presented limited metastatic disease apart from a cardiac metastasis. The initial diagnosis was challenging and was facilitated by functional imaging with an immune positron emission tomography-computed tomography scan (PET-CT) using an anti-CEA bispecific antibody and a 68Ga-labeled peptide. Both patients were treated with the multitarget kinase inhibitor vandetanib with prolonged stability. The first patient was alive at the last follow-up, 14 years after the diagnosis of cardiac metastasis. The second patient required surgical excision of the cardiac mass because of disease progression under vandetanib.

Conclusion: These cases illustrate long-term survival and effectiveness of clinical management of two patients who developed cardiac metastases from MTC, in the current era of personalized medicine with targeted therapy.

Gundogan BD, Sagcan F, Bozdogan ST, Balci Y, Daloglu FT, Citak EC. Vandetanib in a Child Affected by Neurofibromatosis Type 1 and Medullary Thyroid Carcinoma with Both NF1 and Homozygous RET Proto-oncogen Germ-line Mutations. J Clin Res Pediatr Endocrinol. 2021 Aug 23;13(3):342-6 (18).

Background: Neurofibromatosis type 1 (NF1) is a common, autosomal dominant, multi-systemic neurocutaneous disorder. Medullary thyroid carcinoma has not been reported yet in patients with NF1 mutation.

Case: A 15-year-old male patient was diagnosed with both NF1 and MTC, and who had mutations in both NF1 and RET genes. Molecular testing revealed a heterozygous mutation in NF1 gene and a homozygous mutation in codon 891 in the RET gene. The patient had total thyroidectomy and radical neck dissection. Due to incomplete removal of lymph nodes and remaining thyroid tissue, vandetanib treatment was initiated at a dose of 300 mg/day for two years and serum calcitonin and CEA levels gradually decreased and reached the normal reference range.

Conclusion: Although vandetanib has been shown to improve progression-free survival in adults with advanced MTC, data in pediatric patients are limited. Herein, we report the use and outcome of vandetanib in a pediatric MTC case in which NF1 gene and RET proto-oncogene mutation were identified together.

6.2. BENEFIT EVALUATION

Medullary thyroid cancer is a rare cancer (2.1% of all types of thyroid cancers) (1). Most patients (80% to 90%) are RET-positive, 10% to 20% are RET negative/RAS mutant and in the remaining patients no mutation is identified (4). In routine clinical practice, RET mutation status is rarely evaluated prior to the treatment.

Surgical resection of MTC is the primary treatment. For unresectable, recurrent, or symptomatic and progressing MTC, preferred options are vandetanib and cabozantinib as per international guidelines. There is no head-to-head study comparing vandetanib versus cabozantinib.

Vandetanib is an effective first-line treatment option for unresectable, advanced metastatic MTC. In daily practice, young patients and those having symptomatic MTC at treatment initiation appear to be long responders to vandetanib (12) (13).

The activity of vandetanib in RET positive patients is well established in the pivotal phase III study (ZETA) (11) and its recent addendum to CSR (described in Section 7.3.3.1):

• The overall response rate (ORR) was 51.7% with vandetanib versus 14.9% with placebo.

• The hazard ratio for PFS, primary end-point, was 0.46 [95% CI 0.29-0.74] with a 2-year PFS rate of 55.7% with vandetanib versus 40.1% with placebo.

A reanalysis of tissue samples of 69 patients lacking M918T mutation was conducted in ZETA study using new methodologies. Of these 69 patients, 52 were reclassified as being RET mutant, 14 patients were RET negative/RAS mutant (9 treated with vandetanib and 5 treated with placebo), 1 patient treated with vandetanib was RET negative/BRAF mutant and 2 patients (1 in each arm) had no mutation identified (described in Section 7.3.3.1). The activity of vandetanib in these 17 RET negative patients remained

numerically higher than placebo:

• An objective tumor response was observed in 18.2% (2/11 RET negative patients; 2/9 RAS mutant patients) treated with vandetanib versus none of those treated with placebo (n = 6). Both patients had a concomitant decline of CEA and/or calcitonin serum levels.

• The PFS HR was 0.21 (95% CI 0.03-1.53) with a two-year PFS rate of 90% with vandetanib versus 50% with placebo.

• The only RET negative patient who died from thyroid cancer received the placebo.

• The safety profile of vandetanib was not influenced by RET status.

The non-interventional PASS (OBS14778 - Described in Section 7.3.3.2) also included 79 patients treated with vandetanib (21 RET negative, 58 RET positive), most of them coming from ZETA study (n=47/79):

• The objective tumor response in RET negative patients was 9.5% (n=2/21; both patients being RAS positive and coming from ZETA study) and 39.7% (n=23/57) in RET positive patients.

• However, the duration of treatment (27.6 vs 23.4 months in RET negative vs RET mutant), the Disease Control Rate (DCR; 85.7% vs 87.9%), and PFS (35.7 vs 25.4 months) were not influenced by RET status. Cancer death was lower in RET negative patients (4.8%) than in RET mutant patients (13.8%).

Considering that vandetanib is indicated for patients with aggressive and symptomatic MTC, that vandetanib shows objective responses in RAS mutant patients (main subgroup of RET negative patients), that the safety profile of vandetanib is not influenced by RET status, that there is currently no treatment alternative to vandetanib in most European countries and that most recent technologies to determine RET status are not available or not reimbursed everywhere, the MAH considers that the benefit/risk balance of vandetanib remains positive regardless of RET status.

CHMP rapporteur's comment:

The applicant's view that the benefit/risk balance of vandetanib remains positive regardless of RET status is not shared. The assessment of this benefit/risk ratio in RET negative patients is part of the procedure under investigation **EMEA/H/C/002315/II/0043**.

6.3. SAFETY

Pharmacovigilance inspections

For local pharmacovigilance (PV) inspections:

One (1) PV inspection was carried out in France in the period 20 May 2021 to 19 May 2022.

For Global Pharmacovigilance (GPV) inspections:

One (1) PV inspections of the Sanofi GPV system took place in the period of 20 May 2021 to 19 May 2022.

Table 1 - History of pharmacovigilance system inspection

Inspection start Date	Inspection end date	Inspected Site	Competent Authority	List of products concerned for this inspection
27-Sep-2021	01-Oct-2021	GPV-Bridgewater USA	FDA	All Sanofi pharma and Sanofi Pasteur products approved in USA with 3 product entry points: DUPIXENT®(Dupilumab), CAPRELSA® (Vandetanib) and SARCLISA®(Isatuximab)

GPV: Global Pharmacovigilance; USA: United States of America; FDA: Food and Drug Administration.

Conclusion:

The findings observed during the above regulatory PV inspections conducted in the period of 20 May 2021 to 19 May 2022 did not have any potential or known influence on the benefit-risk balance for vandetanib.

Worldwide marketing approval status

CAPRELSA is approved in more than 40 countries worldwide.

Actions taken in the reporting interval for safety reasons during the period covered

On 29 September 2021 (eCTD Sequence No. 0248), prior approval labeling supplement was submitted to the United States (US) FDA with the revisions to warning and precautions, adverse reactions, use in specific population sections, and the medication guide regarding renal failure and wound healing complications. On 01 March 2022, Sanofi received information request (IR) by email from Safety Regulatory Project Manager and Sanofi submitted the proposed labeling comments edits to the United States Prescribing Information (USPI) and medication guide in response to the Agency comments by email on 10 March 2022 and followed by formal submission on 16 March 2022 (eCTD Sequence No. 0252). On 18 March 2022, Sanofi received IR by email form the Safety Regulatory Project Manager and Sanofi submitted the proposed labeling comments edits to the USPI and medication guide in response to the agency comments on 28 March 2022 (eCTD Sequence No. 0253). On 28 March 2022, FDA approved S-019.

PRAC Rapporteur assessment comment

Caprelsa EU SmPC has been updated with information on renal failure (sections 4.2 and 4.4) and on impaired wound healing (section 4.4) within assessment of the variation **EMEA/H/C/002315/II/0052** and of the **EMEA/H/C/PSUSA/00009327/202104** procedure.

For EU, on the 28 June 2021, MAH received a formal request for supplementary information from CHMP after reviewing the OBS14778 PASS report aimed at switching the conditional EU approval to a regular one. The authority requested the following information:

• To elaborate on differences in response rate initially reported at the time of approval and those reported in the PASS study.
• To provide some clarifications on RET mutation analyses performed at the time of approval and in the

PASS study (details on patient disposition and patient flow over time; confirm how many patients lacking M918T mutation at the time of approval were confirmed to be RET negative following re_analysis of RET status).
• To discuss the benefit-risk in the RET negative population given the known substantial toxicity profile of CAPRELSA.

The answer that was submitted 13 October 2021 stated that considering the post-hoc re-analysis of the pivotal Study D4200C00058 (LPS14811) the benefit-risk profile of vandetanib is considered acceptable in RET-negative patients with unresectable locally advanced or metastatic MTC with an ORR of 18.2% with vandetanib versus 0% with placebo and a PFS rate at two years of 90% with vandetanib versus 50% with placebo. Interestingly, RET-negative patients having an objective tumor response with vandetanib had a concomitant RAS mutation. These patients represent the majority of RET-negative patients. No new safety signal was observed in RET-negative patients. Thus, Sanofi believes that the benefit/risk balance of vandetanib remains positive in the currently approved indication regardless of the RET status and vandetanib should not be contraindicated in RET-negative patients with MTC. Sanofi proposed to provide addendum reports to the two studies (OBS14778 and D4200C00058) as soon as possible and, based on the re-analysis of RET mutation status recently performed, to update more adequately the Section 5.1 of the SmPC regarding the RET-negative patients.

On the 17 December 2021 another assessment report was received concluding that the efficacy of CAPRELSA was not sufficiently established in RET negative patients. Considering the known substantial toxicity of CAPRELSA, the benefit-risk balance was considered negative for RET negative patients. Sanofi was thus requested to restrict the indication to RET positive patients. The answer to this second request was submitted on 18 March 2022. Sanofi submitted the CSR addendum and concluded that based on the provided clinical and literature data that based on the provided clinical and literature data, discrepancies in RET testing quality between institutions as well as the lack of standard of care for RET negative patients, vandetanib should remain a treatment option for patients with aggressive, symptomatic, unresectable, locally advanced or metastatic MTC.
Another assessment report was received last 16 May 2022, requesting to restrict the use of CAPRELSA to RET positive patients. Sanofi is working on the answer.

On the basis of information available, no other actions for safety reasons were taken in the reporting interval, related to investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities and which had:

• A significant influence on the risk-benefit balance of the authorized medicinal product; and/or
• An impact on the conduct of a specific clinical trial(s) or on the overall clinical development program

PRAC rapporteur assessment comment
At the DLP for this renewal, the assessment of the variation **EMEA/H/C/002315/II/0043** was ongoing and a CHMP opinion is expected in September 2022.

Significant changes to reference safety information

The Reference Safety Information (RSI) used at the beginning of the period was Company Core Data Sheet (CCDS) version 3, dated 19 September 2019.

The following changes were made:

WARNINGS section: Following was added with editorial changes:

Renal failure

Cases of renal failure have been reported in patients treated with vandetanib. Dose interruptions, adjustments, or discontinuation may be necessary.

The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to 50 mL/min) renal impairment and monitor the QT interval closely. Vandetanib is not recommended for use in patients with severe renal impairment (clearance below 30 mL/min).

There is no information available for patients with end-stage renal disease requiring dialysis.

Impaired wound healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, vandetanib has the potential to adversely affect wound healing.

Withhold vandetanib for at least one month prior to elective surgery. Do not administer vandetanib for at least two weeks following major surgery and until adequate wound healing. The safety of resumption of treatment with vandetanib after resolution of wound healing complications has not been established.

In the adverse drug reactions (ADRs) section, "impaired healing and renal failure" were added.

The RSI in use at the data lock point (DLP) is CCDS version 4, dated 26 August 2021 attached in Appendix 1.1.

The significant differences between global labeling document ie CCDS for vandetanib version 4 dated 26 August 2021 and the current EU SmPC for vandetanib dated 30 May 2022 have been presented in Appendix 1.2.

PRAC Rapporteur assessment comment

Caprelsa EU SmPC has been updated with information on renal failure (sections 4.2 and 4.4) and on impaired wound healing (section 4.4) within assessment of the variation **EMEA/H/C/002315/II/0052** and of the **EMEA/H/C/PSUSA/00009327/202104** procedure.

Estimated exposure and use patterns

Cumulative exposure in clinical trials

Overall, 4729 subjects (4532 patients, 197 healthy subjects) have received vandetanib as an investigational product.

Cumulative and interval patient exposure from postmarketing experience

The interval worldwide patient exposure to vandetanib is estimated to be approximately 1632 patients, including 908 patients in EU countries.

The global cumulative exposure to vandetanib from 06 April 2011 through 31 May 2022 is estimated to be approximately 15 375 patients. In addition, 20 patients were exposed to vandetanib in the Named Patient Supply programs.

Estimation of paediatric population exposure to vandetanib in EU

The estimated paediatric patient interval exposure to CAPRELSA in Europe is 90 patients.

Data in summary tabulations

- **Cumulative summary tabulations of serious adverse events from clinical trials:**

PRAC Rapporteur assessment comment

Cumulatively, 4,491 Serious Adverse Events (SAEs) were reported from MAH-sponsored clinical trials, 3,386 were reported with vandetanib, 625 with active comparator, 265 with placebo. For 85 SAEs, IMP is still blinded and for 130 SAEs no IMP was given.

- **Cumulative and interval summary tabulations from postmarketing data sources:**

PRAC Rapporteur assessment comment:

Cumulatively, 5,646 ADRs have been reported with vandetanib, 510 of which were reported during the present reporting period:

- spontaneous sources: 122 serious ADRs and 362 non serious ADRs;
- solicited sources: 26 serious ADRs.

The 3 leading SOCs as well as the serious ADRs reported from spontaneous sources, were:

General disorders and administration site conditions: n = 18 serious ADRs: disease progression (2), death (6), asthenia (2), fatigue (2), condition aggravated (1), Critical illness (1), drug ineffective (1), pain (1), Performance status decreased (1) and Pyrexia (1).

Infections and infestations: 14 serious ADRs: Pneumonia (5), Hepatitis A (2), Bronchitis (1), Clostridium difficile infection (1), Colonic abscess (1), Conjunctivitis (1), Diverticulitis (1), Sepsis (1) and Tooth infection (1).

Skin and subcutaneous tissue disorders: 12 serious ADRs: Photosensitivity reaction (2), Alopecia (1), Dermatitis bullous (1), Epidermal necrosis (1), Erythema multiforme (1), Hair texture abnormal (1), Nikolsky's sign (1), Rash erythematous (1), Skin lesion (1), Trichorrhexis(1) and Toxic epidermal necrolysis (1).

A new case of TEN (Toxic Epidermal Necrolysis) from post-marketing sources has been received during the reporting period. Within **EMEA/H/C/PSUSA/00009327/202204** procedure, the MAH has been requested to review cumulatively events of TEN reported with vandetanib from all sources. A part from this point, review of the leading SOCs as well as the most frequently reported serious ADRs from spontaneous sources did not raise any comments with regard to vandetanib safety profile / vandetanib therapeutic indication.

Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies

During the reporting period of this ACO, addendum to the CSR of the pivotal study D4200C00058 (dated 10 March 2022) has been prepared which integrates a reanalysis of RET status using new methodologies. An amendment to the non-interventional study OBS14778 has also been performed.

- Addendum to CSR of Study D4200C00058 (LPS14811) "An International, Phase III, Randomized, Double Blinded, Placebo-controlled, Multi-center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer" (Dated 10 March 2022);
- Addendum to the PASS report OBS14778 (D4200C00104) "International Observational Study 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 Medullary Thyroid Cancer" (09 March 2022).

PRAC Rapporteur assessment comment:

Assessment of the addendum to the CSR of Study D4200C00058 (LPS14811) and assessment of the PASS report OBS14778 (also named D4200C00104), are part of the ongoing procedure **EMEA/H/C/002315/II/0043**.

Literature

No publications which contain important safety findings, were identified in the scientific and medical literature.

Overview of Signals

Signal term	Date detected	Status (ongoing or closed)	Date closed (if applicable)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Wound healing complications	Jan/2021	Closed	Jul/2021	Internal Labeling Harmonization	The EMA requested to clarify whether the MAH intends to update SmPC with recommendation on CAPRELSA intake when surgery is planned, to align with the updated USPI. The USPI was updated in 2020 with the risk of impaired wound healing based on the biologic plausibility and the possible class-effect despite insufficient evidence of direct causality with vandetanib. The signal is re-opened to review the new data since the last signal evaluation in 2019 to support the SmPC/CCDS update.	Aggregate review of internal Pharmacovigilance database | Literature review | Review of external spontaneous reporting system data | Review of Pharmacovigilance textbooks | Preclinical data review | Clinical data review | Pharmacodynamic/Pharmacokinetic data review	Label Evaluation | Routine Pharma covigilance
Renal failure	Sep/202	Closed	Sep/202	Internal eRMR	This signal is opened in order	Aggregate review of	Routine Pharma

Signal term	Date detected	Status (ongoing or closed)	Date closed (if applicable)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
	0		1	Review | Literature	to evaluate increased frequency of cases of renal failure reported with the use of vandetanib, picked up from quarterly EVDAS review and one published literature referred below: ref: "Pilco Teran et al. Acute tubulointerstitial nephritis induced by the tyrosine kinase inhibitor vandetanib. Invest New Drugs. 2020 Jul 9". Additionally proteinuria, nephrolithiasis and haematuria are listed events	internal Pharmacovigilance database | Clinical data review | Literature review | Preclinical data review | Review of external spontaneous reporting system data | Review of Pharmacovigilance textbooks	covigilance | Label Evaluation
Drug-induced liver injury	Oct/2021	Closed	Jan/2022	ICSR	The case of drug-induced liver injury and simultaneous hepatitis requires full assessment based on review of global PV database, worldwide literature, external databases, as well as review of biological plausibility.	Aggregate review of internal Pharmacovigilance database | Clinical data review | Literature review | Review of external spontaneous reporting system data | Review of Pharmacovigilance textbooks	Routine Pharma covigilance
Wound healing complications	Jan/2021	Closed	Sep/2021	Internal Labeling Harmonization	The signal was first evaluated and refuted in 2019. Despite insufficient evidence of direct causality with vandetanib mainly due to a small number of case reports in the PV database for this very rare cancer type, the USPI was	Aggregate review of internal Pharmacovigilance database | Literature review | Review of external spontaneous reporting system data | Review of Pharmacovigilance textbooks |	Routine Pharma covigilance | Label Evaluation

Signal term	Date detected	Status (ongoing or closed)	Date closed (if applicable)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					updated in 2020 with the risk of impaired wound healing and the recommended duration of drug withholding before and after surgery based on the biologic plausibility and the possible class-effect as per the FDA request. The signal was reopened for evaluation in Feb 2021 after the EMA requested to clarify whether the MAH intends to update SmPC to be aligned with the USPI. The signal was again refuted for the same reason, but the SMT recommended the label review and update for the sake of labeling harmonization. The CCDS/SmPC updates were proposed at the LRC on June 10 2021, but the team was requested to re-evaluate the signal if the label revision is expected, since refuted signals cannot be reflected in the labels. The signal is reopened this time to support CCDS/SmPC updates based on the biological plausibility and the class effect	Preclinical data review	
Cortisol increased	Jan/2021	Closed	Sep/2021	PRAC Signal |	evaluation requested by	Aggregate review of internal	Routine Pharma covigilan

Signal term	Date detected	Status (ongoing or closed)	Date closed (if applicable)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
				Literature	preliminary PSUR assessment report	Pharmacovigilance database | Clinical data review | Literature review | Review of external spontaneous reporting system data | Review of Pharmacovigilance textbooks	ce

PRAC Rapporteur assessment comment:
Assessment of the signal of Drug induced liver injury is ongoing within **EMEA/H/C/PSUSA/00009327/202204** procedure.

Relevant information on medication errors

There were no relevant safety findings on patterns of medication errors and potential medication errors" that have been identified during the present reporting period and would require specific risk minimization measures (RMMs).

Summary of the PSUR safety concerns

Summary of safety concerns	
Important identified risks	Posterior reversible encephalopathy syndrome (also known as Reversible posterior leukoencephalopathy syndrome) QTc prolongation and Torsades de pointes Cerebrovascular events Cholelithiasis Diarrhea Heart failure Hypertension Infections Interstitial lung disease Intestinal perforation and/or obstruction Pancreatitis Phototoxicity Pneumonia_ Renal toxicity

Summary of safety concerns	
	Toxic epidermal necrolysis, toxic skin eruption, exfoliative dermatitis, and other skin reactions
Important potential risks	Teeth and bone abnormalities in the paediatric population Medication errors related to paediatric population Hepatic failure Reproductive toxicity
Missing information	Long-term use Use during pregnancy Use in elderly patient population Use in non-Caucasian patient population Use in patients with cardiac impairment Use in patients with hepatic impairment Use in patients with moderate to severe renal impairment

PRAC rapporteur assessment comment

Within **EMEA/H/C/PSUSA/00009327/202204** procedure, the MAH has been requested to review cumulatively events of TEN reported with vandetanib from all sources. Apart from this point, no significant new information regarding important identified /potential risks associated to vandetanib was received during this reporting interval.

The MAH has been also requested, for the next PSUR to review the list of PSUR safety concerns for vandetanib in order to propose the removal of the most well-known and characterised safety concerns that would not warrant a review in each PSUR (e.g. diarrhoea, phototoxicity, etc.).

6.4. DISCUSSION

Clinical expert statement

The positive benefit/risk profile of vandetanib already established in RET mutant patients in a pivotal phase III study is confirmed. The objective response observed with vandetanib is RET negative patients may be lower than in RET mutant patients but remains numerically higher than placebo. Moreover, PFS, DCR and the duration of treatment appear comparable regardless of RET status and cancer death rate appears lower in RET negative patients compared to RET mutant patients. Considering that vandetanib is indicated for patients with aggressive and symptomatic MTC, that vandetanib shows objective responses in RAS mutant patients (main subgroup of RET negative patients), that the safety profile of vandetanib is not influenced by RET status, that there is no treatment alternative to vandetanib in many European countries (cabozantinib is not reimbursed for MTC in most European countries), and that most recent technologies to determine RET status are not available or not reimbursed everywhere, the MAH considers that the benefit/risk balance of vandetanib remains positive regardless of RET status.

CHMP rapporteur's comment:

No new safety concerns or change in benefits have been identified during the assessment of the annual renewal of the conditional marketing authorisation for vandetanib.

Based on the available safety and efficacy data to date for vandetanib, the overall benefit-risk profile of vandetanib remains positive in aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease under the current recommended conditions of use.

However, the applicant's view that the benefit/risk balance of vandetanib remains positive regardless of RET status is not shared. The assessment of this benefit/risk ratio in RET negative patients is part of the procedure under investigation **EMEA/H/C/002315/II/0043**.

7. Risk management plan

No change of the RMP is proposed yet: as written in a previous communication with EMA in 2020, the MAH will provide an updated RMP upon approval of the on-going type II variation **EMEA/H/C/002315/II/0043.**

8. Changes to the Product Information

No changes to the Product Information (PI) are introduced with this renewal procedure.