<Date>

Direct Healthcare Professional Communication

Caprelsa® (vandetanib): Restriction of indication

Dear Healthcare Professional,

Sanofi in agreement with the European Medicines Agency (EMA) and the <National Competent Authority> would like to inform you of the following:

Summary

- **Vandetanib should not be administered to patients in whom rearranged during transfection (RET) mutation status is not known or is negative.**
- **Restriction of the indication is based on data from the randomized study D4500C00058, and the observational study OBS14778, showing insufficient activity of vandetanib in patients with no identified RET mutations.**
- **Prior to initiation of treatment with vandetanib, the presence of a RET mutation should be determined by a validated test.**
- **For patients currently under treatment and for which the RET status remains unknown or is negative, healthcare professionals are recommended to discontinue treatment taking into account their judgement of the patients' clinical response and the best treatment available.**

Background information

In 2012, a conditional marketing authorization (CMA) was granted for vandetanib for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. The indication was based on the randomized, double-blind, placebo-controlled Study D4200C00058 (referred as Study 58) [1].

In Study 58, RET mutation testing at time of CMA was performed by using the polymerase chain reaction (PCR) based Amplification Refractory Mutation System (ARMS) assay for the M918T mutation, and direct sequencing of DNA for mutations in exons 10, 11, 13, 14, 15 and 16 (site of M918T mutation) on all sporadic patients where DNA was available (297/298). RET mutation status was positive in 187 patients (56.5%), unknown in 138 (41.1%), and negative in 8 patients (2.4%), including 2 patients in the vandetanib group. Due to the very limited number of patients without a RET mutation, a correlation between RET mutation status and clinical outcome could not be evaluated. The following information was added in the SmPC section 4.1 at time of CMA: *"For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision".*

In order to better characterize the benefit/risk in RET mutation negative patients, Sanofi conducted study D4200C00104 (OBS14778), an observational study evaluating vandetanib in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, and locally advanced/metastatic MTC and proceeded to a re-analysis of the RET status in study 58, using the most recently developed methodologies.

RET status reanalysis in study 58

A re-analysis was performed on the samples of 79 patients who were previously categorized as RET mutation "unknown". Re-analysis was performed with a custom Taqman assay to genotype the RET M918T mutation and, when adequate material was available, sequencing using Illumina technology was undertaken to reveal any other RET mutations. Of the 79 patients with unknown RET mutation status, 69 had enough tissue sample to allow re-analysis. Most patients were reclassified as RET mutant (52/69), while 17/69 patients had no RET mutation detected. Patients reclassified as RET mutant were pooled with those patients initially identified as RET mutant, leading to a total number of 239 RET mutant patients (172 treated with vandetanib and 67 treated with placebo). Of the 17 RET mutation negative patients, 11 were treated with vandetanib and 6 with placebo. Using blinded central review of imaging, overall response rate (ORR) was 51.7% in the vandetanib group compared to 14.9% in the placebo group in patients with a RET mutation. At 2 years, 55.7% of RET mutant positive patients treated with vandetanib had no disease progression versus 40.1% of RET mutant positive patients treated with placebo. In the RET mutation negative patients, ORR was 18.2% in the vandetanib group (response in 2 out of 11 patients) and 0% in the placebo group (response in 0 out of 6 patients). The two RET mutation negative patients with a response to vandetanib were carrying a RAS mutation. At 2 years, 90% of RET mutant negative patients treated with vandetanib had no disease progression versus 50% of RET mutation negative patients treated with placebo [2].

RET status analysis in study OBS14778
In study OBS14778, data from 47 patients treated with vandetanib from study 58 who had their RET status re-analysed, were pooled with 50 prospectively and retrospectively enrolled patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. Overall, 97 patients were screened and 79 were evaluable for efficacy, of which 58 were RET mutation positive and 21 were RET mutation negative. ORR was 5.0% for RET mutation negative patients and 41.8% for RET mutation positive patients. When using blinded central review for the RET negative patients included in Study 58, ORR was 9.5%

In view of the above data, the activity of vandetanib is considered insufficient to outweigh the risks associated with vandetanib treatment in RET mutation negative patients.

Consequently, the indication of vandetanib (included in section 4.1 of the SmPC) is being restricted to RET mutant patients, and it will appear as follows:

"Caprelsa is indicated for the treatment of aggressive and symptomatic 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".

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in patients receiving vandetanib.

Healthcare Professionals should report any adverse reactions or any off-label use with or without adverse reactions suspected to be associated with the use of Caprelsa (vandetanib) in accordance with the national

spontaneous reporting system: *<Insert local contact information>.*

To be modified dependent on country: <Details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

References:

[1] Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III Trial. J Clin Oncol 2011; 30 (2):134-141.

[2] CAPRELSA EMA Summary of Product Characteristics (Section 5.1-Table 4- *Available from…relevant link to be included upon publishing of approved texts….)*

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product/active substance **Marketing authorisation holder**	Caprelsa (Vandetanib) 100 mg film coated tablets and 300 mg film-coated tablets Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands
Safety concern and purpose of the communication	The purpose of the communication is to alert healthcare professionals that the indication of Caprelsa is being restricted only to patients with an identified RET mutation since based on available data from Study D4500C00058 and Study OBS14778, the activity of Caprelsa is considered insufficient in patients with no identified RET mutation.
DHPC recipients	HCPs involved in prescribing and handling of Caprelsa® (e.g. medical oncologists-medical oncologists treating also paediatric patients / nurses, hospital oncologists-hospital oncologists treating also paediatric patients / nurses / pharmacists /endocrinologists). Target groups should be further defined on national level, depending on national health care systems.
Member States where the DHPC will be distributed	All EEA member states where Caprelsa is marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP/CMDh	15/09/2022
Submission of translated DHPCs to the national competent authorities for review	Within 10 days after EC Decision
Agreement of translations by national competent authorities	According to the timelines set by NCAs (generally withing 5 working days)
Dissemination of DHPC	Within 2 weeks after respective NCA approval