Direct Healthcare Professional Communication

7th April 2023

Caprelsa® (vandetanib): Restriction of indication

Dear Healthcare Professional,

Sanofi in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) 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 to section 4.1 of the SmPC when the CMA was granted: *"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). This was 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

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

You can report via:

- the Yellow Card website – https://yellowcard.mhra.gov.uk/
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals.

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Suspected adverse reactions can also be reported to Sanofi. Tel: 0800 0902314. Email: UKdrugsafety@sanofi.com. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact point

Should you have any questions or require additional information, please contact **Medical Information** at Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT

Tel: 0800 035 2525

Email: uk-medicalinformation@sanofi.com

Yours faithfully,

Debbie Woods

Head of Medical

General Medicines UK and Ireland

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 100mg Summary of Product Characteristics (Section 5.1-Table 4- *Available from: https://www.medicines.org.uk/emc/product/3944/smpc)*

[3] CAPRELSA 300mg Summary of Product Characteristics (Section 5.1-Table 4- *Available from: https://www.medicines.org.uk/emc/product/7590/smpc)*