נובמבר 2024

צוות רפואי נכבד,

<u>הנידון: צמצום התוויה עבור התכשיר Caprelsa (vandetanib)</u>

חברת סאנופי בע"מ, בשיתוף משרד הבריאות, מבקשת לעדכנך לגבי המידע הבא על התכשיר שבנדון.

המידע כלול בעלוני התכשיר העדכניים.

<u>להלן עיקרי הדברים:</u>

- צמצום ההתוויה למטופלים החיוביים למוטציית rearranged during transfection (RET) בלבד.
- אין לתת טיפול ב- vandetanib למטופלים בעלי מוטציית RET שאינה ידועה או שלילית.
- צמצום ההתוויה מבוסס על נתונים מהניסוי האקראי D4500C00058 והמחקר התצפיתי OBS14778, המראים כי היעילות של vandetanib אינה מספקת במטופלים שבהם לא זוהו מוטציות RET
- לפני התחלת הטיפול ב-vandetanib יש לבדוק את נוכחות מוטציית RET על ידי בדיקה מתאימה.

עבור מטופלים הנמצאים כעת תחת טיפול בתכשיר ואשר סטטוס מוטציית ה-RET אינו ידוע או שלילי, מומלץ כי הצוות הרפואי יפסיק את הטיפול, זאת תוך התחשבות בשיקול הדעת לגבי תגובתו הקלינית של המטופל, וכן זמינותם של קווי הטיפול הטובים ביותר.

למידע נוסף אודות התכשיר, יש לעיין בעלון לרופא העדכני המאושר.

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 SPC 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 SPC) is being restricted to RET mutant patients, and it will appear as follows:

"Caprelsa is indicated 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."

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 in patients taking Caprelsa (vandetanib) to the Ministry of Health by using the online reporting form available in the following link: https://sideeffects.health.gov.il.

Additionally, should be reported to Sanofi Israel Pharmacovigilance: PV.Israel@sanofi.com

Company contact point

Should you have any question or require additional information, please contact us at: 09-8633081 or at Sanofi Medical department: medical.israel@sanofi.com.

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 SPC (Section 5.1-Table 3)

בברכה,

חברת סאנופי ישראל בע"מ