Docusign Envelope ID: 1ABAB8AD-08D6-4B36-8677-B5F6BA3CFF61

Direct Healthcare Professional Communication

Gavreto® 100 mg hard capsules

December 2024

הנדון: סיכון לזיהומים חמורים וקטלניים בטיפול עם התכשיר Gavreto (Pralsetinib)

צוות רפואי נכבד,

חברת רוש פרמצבטיקה (ישראל) בע"מ, בשיתוף עם משרד הבריאות, מעוניינת להביא לידיעתך את המידע הבא הנוגע לבטיחות השימוש בתכשיר Gavreto (Pralsetinib).

להלן עיקרי הדברים:

- זיהומים חמורים וקטלניים, כולל זיהומים אופורטוניסטיים, דווחו בחולים שטופלו ב- Gavreto.
- יש לנטר באופן הדוק אחר סימנים ותסמינים של זיהום ולטפל כנדרש.
- יש להשהות את הטיפול ב- Gavreto בנוכחות זיהום פעיל. יש להפסיק לצמיתות את הטיפול ב- Gavreto במצב של זיהום מסכן חיים.

Background on the safety concern

Pralsetinib is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
In the ongoing phase III trial AcceleRET-Lung (BO42864, NCT04222972)[1], a randomized, open label study of pralsetinib versus standard of care (SOC) in first-line treatment of RET fusion-positive, metastatic non-small cell lung cancer (NSCLC) patients, an ad hoc analysis has demonstrated an imbalance regarding the risk of severe and fatal infection, including severe opportunistic infections, between the pralsetinib and SOC arms. The ad hoc analysis was triggered by an observation of an imbalance in fatal adverse events between the two treatment arms, primarily due to infections. Fatal adverse events were reported in 14 patients (13.0%) in the pralsetinib arm, versus 5 patients (4.8%) in the SOC arm. Of these fatal events, fatal infection events occurred in 5 patients (4.6%) in the pralsetinib arm, and none in the SOC arm. Non-infection fatal AEs in the pralsetinib arm did not reveal any particular pattern.

At the time of the ad hoc review, 212 patients had received at least any amount of any study treatment, 108 patients in the pralsetinib arm, and 104 patients in the SOC arm. Severe (grade 3-5) infection events occurred in 28 (25.9%) pralsetinib treated patients versus 8 (7.7%) patients receiving SOC. Statistical analysis performed on severe infection adverse events demonstrate a significant imbalance, with Fisher's exact two-tailed p-value of 0.0004. The risk ratio, calculated using the Aalen-Johanssen estimator[2] taking into account variable time on treatment and competing events, indicated a significantly higher risk of severe infection with pralsetinib vs SOC treatment (risk ratio 3.33; 95% CI: [1.57, 7.06], with the lower limit of the 95% CI > 1). Half of the severe infections in pralsetinib treated patients

Roche Pharmaceuticals (Israel) Ltd.
Drug Safety
6 Hacharash St.
P.O.B. 6391
Hod Hasharon 4524079
Tel. + 972-9-9737777
Fax + 972-9-9737850

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occurred within the first 66 days of treatment. Approximately half of the severe infections were lung infections. Most severe infections were not preceded by neutropenia or lymphopenia. Fatal infections occurred in 5 (4.6%) patients in the pralsetinib arm, and in 0 patients in the SOC arm. Severe opportunistic infections, including pneumocystis jirovecii pneumonia, cytomegalovirus pneumonia, legionella pneumonia and esophageal candidiasis occurred in 7 (6.5%) of pralsetinib treated patients, and in 0 patients receiving SOC.

This data supports concluding that severe infections, including opportunistic infections, warrants an update to the Product Information in Warnings and Precautions, to alert prescribers and patients of this risk.

The corresponding updates to the product label will be forthcoming.

Prescriber Action

Monitor patients closely for signs and symptoms of infection, and treat appropriately according to local/institutional guidelines. Ensure patients are up to date on vaccinations according to local/institutional guidelines.

Withhold Gavreto in the presence of active infection, and resume with dose reduction following labeled prescribing information when infection resolves. Permanently discontinue Gavreto in the setting of life-threatening infection.

Call for reporting

Healthcare professionals should report any adverse events, which are suspected to be associated with the use of Gavreto, to the Israeli Ministry of Health by using an online form: https://sideeffects.health.gov.il
It could also be reported to Roche Israel drug safety department at 09-9737722 or israel.drugsafety@roche.com.

Company contact point

Should you have any questions regarding the use of Gavreto, please feel free to contact us at:

Roche Pharmaceuticals (Israel) Ltd.,
Israel.drugsafety@roche.com
09-9737777.

Annexes

References

1. https://clinicaltrials.gov/search?intr=NCT04222972
2. Stegherr et al. Trials. 2021 Jun 29;22(1):420. doi: 10.1186/s13063-021-05354-x. PMID: 34187527; PMCID: PMC8244188

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Yours sincerely,

Tamar Birenboim-Gal

Lavi Amiad

Dr. Tamar Birenboim-Gal
Medical Director

Lavi Ami-Ad
Qualified Person for Pharmacovigilance

Roche Pharmaceuticals (Israel) Ltd.
Drug Safety

6 Hacharash St.
P.O.B. 6391
Hod Hasharon 4524079

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