From: Gayane Ghazaryan

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TECENTRIQ® (atezolizumab), Identified Risk of Severe Cutaneous Adverse Reactions (SCARs) Direct Healthcare Professional Communication (DHPC)

Dear Healthcare professional,
Hoffmann-La Roche in agreement with European Medicines Agency and the Scientific Centre of Drug and Medical Technology Expertise after academician Emil Gabrielyan would like to inform you of the following:

Summary

- Severe Cutaneous Adverse Reactions (SCARs) are rare but potentially fatal skin toxicities frequently associated with drug use including immune checkpoint inhibitor, as a class. A comprehensive analysis of the data available across the TECENTRIQ (atezolizumab) program has identified cases of SCARs following atezolizumab use.
- SCARs were previously known to be potentially associated with the use of atezolizumab, and have been monitored continuously. Based upon the totality of evidence in a recent analysis, SCARs are now considered to be an identified risk for atezolizumab.
- Consequently, the local label will be updated to reflect guidance for discontinuation of TECENTRIQ (atezolizumab), to add a Warning and Precaution and to update the known Adverse Drug Reaction table.
- The benefit-risk of atezolizumab as monotherapy, or as part of combinations in approved indications remains favourable.

Background on the safety concern

SCARs are a heterogeneous group of immunologically mediated drug eruptions. Although rare, these events are potentially fatal, and are mainly constituted by acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). As per

epidemiology data, the incidence of SJS and TEN ranges from 0.8 to 5.3 and 1.2 to 6 per million person-years respectively[1,2].

A cumulative analysis of the company safety database across the TECENTRIQ (atezolizumab) program identified 99 cases, of which 36 cases of SCARs were confirmed by histopathology or specialist diagnosis, in patients who have received TECENTRIQ (atezolizumab). Approximately 23,654 clinical trial patients and 106,316 patients in post-marketing settings have been exposed to TECENTRIQ (atezolizumab) as of 17 May 2020. The incidence rates of SCAR, regardless of severity, from pooled atezolizumab monotherapy (N=3178) and combination therapy (N=4371) company-sponsored clinical studies was 0.7% and 0.6% respectively. One fatal case of TEN was reported in a 77 year old female patient who received atezolizumab monotherapy.

It is recommended that:

- For suspected SCARs the patients should be referred to a dermatologist for further diagnosis and management
- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

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[1] Li LF, Ma C. Epidemiological study of severe cutaneous adverse drug reactions in a city district of China. Clin Exp Dermatol. 2006;31(5):642-647

[2] Yang MS, Lee JY, Kim J, et al. Incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Nationwide Population-Based Study Using National Health Insurance Database in Korea. PLoS One. 2016;11(11):e0165933

3 Jimenez J, Nardone B, Kosche C, et al. Bullous skin disorders associated with PD-1 and PDL-1 inhibitors: Pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) from the Research on Adverse Drug events And Reports (RADAR) Program. J Am. Acad. Dermatology. 2019; 81(4) supp1

4 Zhao, CY, Hwang, SJ, Consuegra, G et al. Anti-programmed cell death-1 therapy-associated bullous disorders: a systematic review of the literature. Melan Res Volume 28(6), p 491-501.

5. Kamińska-Winciorek G, Cybulska-Stopa B, Ługowskadoi I et al. Review paper Principles of prophylactic and therapeutic management of skin toxicity during treatment with checkpoint inhibitors. Adv. Dermatology Allergology. 2019; 36 (4): 382-391

An update to the local prescribing information to include a Warning and Precaution for SCARs, guidelines for discontinuation and further description of the risk will follow this communication. This DHPC has been disseminated in advance of the local label update to make you aware of the identified risk and to facilitate prompt management of these risks.

Immune mediated cutaneous adverse reactions, including severe reactions, are considered to be a class effect with immune checkpoint inhibitors[3,4,5]. The benefit-risk of atezolizumab as monotherapy, or combination in approved indications remains favourable.

Call for reporting

Health care professionals should report any adverse events suspected to be associated with the use of TECENTRIQ (atezolizumab) to Gayane Ghazaryan, Local Safety Responsible of F.Hoffmann La Roche products in Armenia via following contacts: mob.: +374 91 796688, email: gayaneh.ghazaryan@gmail.com; or back up, Nune Karapetyan via following contacts: mob: +374 91 721153 or email: nune.karapetyan.roche@gmail.com., or direct your reports to Roche Moscow DS Hub via following contacts: tel.: +7-495-229 2999, Fax: +7-495- 229 7999, email: russia.pvhub@roche.com; website: www.roche.ru.

▼ TECENTRIQ (atezolizumab) is subject to additional monitoring. This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

Company contact point

Should you have any questions regarding the use of TECENTRIQ® (atezolizumab), please feel free to contact Gayane Ghazaryan, Local Safety Responsible of F.Hoffmann La Roche products in Armenia via following contacts: mob.: +374 91 796688, email: gayaneh.ghazaryan@gmail.com;
or back up, Nune Karapetyan, via following contacts: mob: +374 91 721153 or email: nune.karapetyan.roche@gmail.com., or direct your reports to Roche Moscow DS Hub via following contacts: tel.: +7-495-229 2999, Fax: +7-495- 229 7999, email: russia.pvhub@roche.com, website: www.roche.ru.

Besides of this, Healthcare professionals are asked to report any suspected adverse reactions according to the local requirements via the national reporting system to the SCIENTIFIC

CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN CJSC via following contacts:
address: 49/4 Komitas av., 0051 Yerevan, Armenia;
HOT LINE: (+ 374 10) 20-05-05, (+374 10) 22-05-05
email: vigilance@pharm.am

Sincerely,

Gayane Ghazaryan, _____ 13.01.2021
Medical Manager, Local Safety Responsible of
Hoffmann-La Roche products in Armenia

Nune Karapetyan _____ 13.01.2021
Commercial Lead of Hoffmann-La Roche products in Armenia