



29th October 2020

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

Dear Healthcare professional,

Roche in agreement with European Medicines Agency (EMA) 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}.

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

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.

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.

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



Call for reporting

Health care professionals should report any adverse events suspected to be associated with the use of TECENTRIQ (atezolizumab) to: cac.farmacovigilancia@roche.com

▼ 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 us at: cac.medical_info@roche.com

Sincerely,

Dra. Alexandra Hambelant
Local Safety Responsible
Roche Servicios S.A.

Dra. Maria Clara Horsburgh
Medical Director
Roche Servicios S.A.