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SAFETY INFORMATION COMMUNICATION

Medical Product category	Title
• **Ethambutol/ Antimycobacterial** • **Cefotaxime/ Beta-lactam antibiotic**	**Risk of Severe Cutaneous Adverse Reactions (SCARs)**

1. Introduction

Reference is made to the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) on updating the product information of Cefotaxime and Ethambutol, respectively, to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and to strengthen advice on Severe Cutaneous Adverse Reactions (SCARs) including DRESS on 5 February and 6 May 2024.[1,2]

Considering the seriousness of the risk of Severe Cutaneous Adverse Reactions (SCARs), the overall safety profile of Ethambutol and Cefotaxime, and the indications for which the medicines are approved. Severe Cutaneous Adverse Reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with Ethambutol and Cefotaxime treatment.[3,4]

It is in this regard that, the Rwanda FDA analysed the risk of Severe cutaneous adverse reactions (SCARs) associated with the use of Ethambutol and Cefotaxime medicines for appropriate regulatory actions, including communicating these important risks to Marketing Authorization Holders (MAH), Healthcare professionals and patients for the adoption of adequate risk minimization measures.

2. Description

Ethambutol is an Antimycobacterial medication primarily used in combination with other drugs to treat tuberculosis. It works by inhibiting the growth of mycobacteria, specifically targeting Mycobacterium tuberculosis. Ethambutol is an antibiotic primarily used to treat tuberculosis. Cefotaxime is an injectable third-generation cephalosporin antibiotic used to treat a variety of bacterial infections.[4]
SCARs including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and DRESS, which can be life-threatening or fatal, have been reported post-marketing in association with Cefotaxime/Ethambutol treatment.

Severe cutaneous adverse reactions (SCARs) to drugs are associated with morbidity, mortality, healthcare costs, and drug development challenges. SCARs to drugs cover a broad spectrum of reactions mainly consisting of Stevens-Johnson Syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms

(DRESS).[5,8] Because of the extensive eruption or the possibility of systemic symptoms, physicians also consider Acute Generalized Exanthematous Pustulosis (AGEP) as SCAR. Early drug withdrawal is mandatory in all SCARs. Physicians' knowledge is essential to improving diagnosis and management and in the limitation and prevention of long-term sequelae.[5,6]

Anti-Tuberculosis Drugs (ATDs) can cause Severe Cutaneous Adverse Reactions (SCARs), such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Underlying tuberculous infection and co-administration of multiple drugs may contribute to the complexity of ATD-related SCARs.[7] Furthermore; beta-lactams are one of the major causative agents of Severe Cutaneous Adverse Reactions (SCARs).

SCAR is a serious and lethal disease, and beta-lactam antibiotic-related SCAR accounts for a large proportion of cases. SJS/TEN, a very severe SCAR with a poor prognosis, was a common type in beta-lactam antibiotic-related SCARs. Cefotaxime is a beta-lactam antibiotic classified as a third-generation cephalosporin.[4] Therefore, more attention should be paid to monitoring skin reactions while using beta-lactam antibiotics and Anti-tuberculosis drugs.

3. *Information to the Patients and Caregivers*

- Patients should be aware of the risk of Severe Cutaneous Adverse Reactions (SCARs) associated with the use of Ethambutol and Cefotaxime products.
- Patients should be advised of the signs and symptoms of skin reactions at the time of prescription.
- Patients should be aware that if the signs and symptoms suggestive of these reactions appear, Cefotaxime/Ethambutol should be withdrawn immediately.
- Patients are advised to report any suspected or encountered adverse event associated with the use of Ethambutol and Cefotaxime products to healthcare professionals and/or to Rwanda FDA using existing reporting channels.

4. *Information to the Healthcare Professionals*

- Healthcare professionals should be aware of the risks of Severe Cutaneous Adverse Reactions (SCARs) associated with the use of Ethambutol and Cefotaxime products.
- Healthcare professionals should be aware that if the patient has developed AGEP, SJS, TEN or DRESS with the use of Cefotaxime/Ethambutol, treatment must not be restarted and should be permanently discontinued.
- Healthcare professionals should be aware that a red, scaly widespread rash with bumps under the skin and blisters is accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalized exanthematous pustulosis).
- In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to Cefotaxime/Ethambutol in children who develop symptoms of rash and fever during therapy with Cefotaxime/Ethambutol.
- Healthcare professionals are requested to collect and submit reports of suspected or encountered adverse events to the Rwanda FDA

5. *Information to the Marketing Authorization Holders/Manufacturers*

- The Marketing Authorization Holders should submit an updated Summary Product Characteristics (SmPC) to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and strengthen advice on Severe Cutaneous Adverse Reactions (SCARs), associated following the use of Ethambutol and Cefotaxime, in the section on warnings and precautions for use and in the section on undesirable adverse reactions once these events are not included yet.

6. *Reporting channel*

Patients and Healthcare Professionals are urged to report any suspected adverse drug event/reaction associated with Ethambutol and Cefotaxime medicines or any other medical product to the Rwanda FDA by using an online reporting tool called **VigiMobile for medicines**, which is available on the Rwanda FDA website at https://vigiflow-eforms.who-umc.org/rw/adr or using online reporting system (PViMS) accessible on https://pvims.rwandafda.gov.rw/security/landing.

Sincerely,

Prof. Emile BIENVENU
Director General

7. *References*

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