RWANDA FDA
Rwanda Food and Drugs Authority

Ref. N°: DD/PVCT/ 4414 /FDA /2025

SAFETY INFORMATION COMMUNICATION

Medical Product category	Title
Sulfamethoxazole, trimethoprim	**Risk of circulatory shock**

1. *Introduction*

Reference is made to Law No. 003/20218 of 09/02/2018 establishing Rwanda FDA, and to the regulations governing pharmaceutical products and medical devices, including IVDs, especially Article 23 on safety information and communication.

Referring to the safety information published in WHO Pharmaceuticals Newsletters No.3,205,(1)(1) further reference is also made to the PRAC's recommendation of the EMA, which has advised updating the product information for combination products of sulfamethoxazole and trimethoprim (also known as cotrimoxazole) to include the risk of circulatory shock(2).

2. *Description*

BACTRIM (sulfamethoxazole and trimethoprim) is a synthetic combination containing an antifolate and sulfa antibiotic, which is available in DS (double strength) tablets, each containing 800 mg sulfamethoxazole and 160 mg trimethoprim; in tablets, each containing 400 mg sulfamethoxazole and 80 mg trimethoprim for oral administration(3).

It is used to treat various infections, such as urinary tract infections (UTIs), ear infections, and lung infections. Other uses include treating infections caused by Pneumocystis jirovecii, Toxoplasma gondii, Stenotrophomonas maltophilia, and community-associated methicillin-resistant Staphylococcus aureus (4). There is also another antibiotic called Septra, which is available as a lower-cost generic. It is taken orally, usually twice daily for most infections. This antibiotic also comes as a suspension called Sulfatrim for people who cannot swallow tablets and as an injection for hospitalized patients.

BACTRIM is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound, and metabolized forms; sulfamethoxazole also exists as the conjugated form. Sulfamethoxazole is metabolized in humans to at least 5 metabolites: The N4-acetyl-, N4-hydroxy-, 5-methylhydroxy-, N4-acetyl5-methylhydroxy- sulfamethoxazole metabolites, and an N-glucuronide conjugate. The formulation of N4-hydroxy metabolite is mediated via CYP2C9. Trimethoprim is metabolized in vitro to 11 different metabolites, of which five are glutathione adducts and six are oxidative metabolites, including the major metabolites, 1- and 3-oxides and the 3- and 4-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms. In vitro studies suggest that trimethoprim is a substrate of P-glycoprotein, OCT1 and OCT2, and that sulfamethoxazole is not a substrate of P-glycoprotein(3).

Sulfamethoxazole/trimethoprim interferes with the bacterial synthesis of tetrahydrofolic acid, an essential stage in the production of thymidine, purines, and subsequently nucleic acids. Sulfamethoxazole inhibits the formation of dihydrofolic acid from p-aminobenzoic acid; trimethoprim inhibits the action of the enzyme dihydrofolate reductase, thus preventing the synthesis of tetrahydrofolic acid from dihydrofolic acid. Thus, the combination of trimethoprim and sulfamethoxazole blocks two consecutive steps within the bacterial metabolic pathway of the biosynthesis of nucleic acids and proteins(5).

Common side effects include nausea, diarrhea, and rash. A rare but serious adverse reaction, TMP-SMX-induced circulatory shock, can occur, resembling septic shock and possibly resulting from a cytokine storm (especially IL-6-mediated). This reaction is more common in HIV-positive or immunocompromised patients(6).

It is against this background that Rwanda FDA communicates these important risks to healthcare professionals and patients for the adoption of adequate risk minimization measures.

3. *Information for the Patients and Caregivers*

- Stop the medication immediately and contact a healthcare provider or seek emergency medical care if you experience Fever and chills, Severe low blood pressure (hypotension), Rapid or irregular heartbeat, Confusion or mental depression, Skin rash, hives, or any other sign of a skin reaction, Difficulty breathing, cough, or chest pain, Severe stomach pain with watery or bloody diarrhea, Unusual bruising, bleeding, or pale skin and Yellowing of the skin or eyes.
- Do not take more of the medication or take it for a longer time than prescribed.
- Drink a full glass (8 ounces) of water with each dose and ensure adequate fluid intake throughout the day to prevent kidney issues like crystalluria.
- Be sure to mention if you have a history of HIV/AIDS, kidney or liver disease, low CD4+ count, heart conditions (especially those requiring AV-node blockers), or electrolyte imbalances, as these can increase the risk of adverse effects.
- Inform your doctor about all other medications you are taking.
- This medication can increase sun sensitivity (photosensitivity). Wear sunscreen, a hat, and protective clothing when outdoors.
- If a severe reaction to this medication has occurred in the past, it should be added to the patient's allergy list to prevent future exposure.
- **Caregivers** should be aware of these symptoms and be prepared to assist the patient in seeking emergency care immediately if a serious reaction is suspected.

4. *Information to Healthcare Professionals*

- Discontinue TMP-SMX immediately at the first appearance of a rash, fever, or any sign of a serious adverse reaction, as these may precede severe systemic issues like circulatory shock.
- Be especially cautious with patients who have **HIV infection** or low CD4+ counts, as they are at a higher risk of severe reactions, **Renal impairment** or underlying disorders of potassium metabolism, **Concomitant use of other hyperkalaemia-inducing drugs**, such as ACE inhibitors, ARBs, or potassium-sparing diuretics (e.g., spironolactone), as this increases the risk of life-threatening hyperkalaemia, which can lead to shock (BRASH syndrome) and A history of any prior TMP-SMX-associated toxicity.
- Monitor complete blood counts, renal function tests (serum creatinine, BUN), and electrolyte levels (especially potassium) frequently, particularly in patients with pre-existing renal issues or those on interacting medications.
- Discontinue the drug if significant electrolyte abnormalities or renal insufficiency is noted.
- If circulatory shock is suspected, discontinue TMP-SMX immediately and institute appropriate management, including intravenous fluid resuscitation and vasopressors if necessary.

- If a patient experiences a shock-like reaction, add TMP-SMX to their allergy list to prevent future exposure, which carries a high morbidity risk.
- Ensure seamless communication between physicians, pharmacists, and nurses regarding patient risk factors, monitoring plans, and prompt reporting of any adverse events to achieve optimal patient outcomes.
- Advise patients to seek immediate medical attention if they experience symptoms like fever, confusion, severe hypotension, rash, difficulty breathing, or irregular heartbeat.
- Report all suspected adverse events associated with the use of carbamazepine to the Rwanda FDA.

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

Rwanda FDA is requesting Marketing Authorization Holders to submit an updated SmPC for sulfamethoxazole and trimethoprim-containing medicines to include the Risk of circulatory shock as an adverse drug reaction. The product label and/or packaging label should also be updated to remind healthcare professionals of the potential effects of sulfamethoxazole and trimethoprim-containing medicines.

6. *Reporting channel*

Patients and Healthcare Professionals are urged to report any suspected adverse drug event/reaction associated with sulfamethoxazole and trimethoprim containing medicines. or any other medical product to 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

- ***References***

1. WHO. WHO Pharmaceuticals 2025. 2025;(1):1–13.
2. Risk P, Committee A, Pharmacovigilance E, Tracking I, Products M, Use H, et al. PRAC recommendations on signals. 2025;31(May):1–6.
3. Pharmacology C. BACTRIM ™ sulfamethoxazole and trimethoprim DS (double strength) tablets and tablets USP.
4. Training C disciplinary. Considerations when prescribing trimethoprim – N : Neurologic effects. 2011;183(16):1851–8.
5. Composition Q. DBL ™ Sulfamethoxazole 400 mg and Trimethoprim 80 mg. :1–20.
6. Liu P, Ranches GP, Gold JA. Trimethoprim-sulfamethoxazole induced circulatory shock in a human immunodeficiency virus uninfected patient : a case report and review. 2018;3:1–5.