Rwanda Food and Drugs Authority
Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
Email: info@rwandafda.gov.rw
website: www.rwandafda.gov.rw

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SAFETY INFORMATION COMMUNICATION

Medicine	Title
Salbutamol	**Potential signal of Anaphylaxis/Anaphylactic shock following the administration of Salbutamol.**

1. *Introduction*

Reference is made to the signal assessment conducted by Rwanda FDA on the potential signal of anaphylaxis/anaphylactic shock following the administration of Salbutamol;
Further reference is made to the Pharmaceuticals and Medical Devices Safety Information No. 381 of March 2021 published by the Japanese Ministry of Health, Labour and Welfare highlighting the risk of shock or anaphylaxis following the administration of Salbutamol sulfate; [1]
Considering the 401 cases recorded in WHO global database (VigiLyze) on "anaphylactic shock/anaphylactic reaction/anaphylactoid shock/anaphylactoid reaction" following the intake of Salbutamol; [2]

It is this regard that Rwanda FDA conducted the assessment of the potential risk of anaphylaxis/anaphylactic shock for appropriate regulatory action including communicating to healthcare professionals of this potential signal.

2. *Description of the safety information*

Salbutamol sulfate is a Beta-2 adrenergic agonist used to treat asthma attacks and exacerbations in adults and children aged 4 years and older, to prevent exercise-induced bronchospasm or before exposure to a known unavoidable allergen challenge, and to treat broncho-asthma and other conditions associated with reversible airways obstruction.[3]
In reversible airway obstruction because of asthma, salbutamol delivers a short-acting bronchodilation with a rapid onset of action. [3]

Anaphylaxis is a severe allergic reaction characterized by skin reactions (including hives, itching, and flushed or pale skin), low blood pressure (hypotension), constriction of the airways and a swollen tongue or throat, which can cause wheezing and difficulty breathing, a weak and rapid pulse, nausea, vomiting, or diarrhea, dizziness or fainting, and other symptoms. [4]
Anaphylactic reactions are classified into two types: immunoglobulin E (IgE) mediated and non-immune (i.e., direct activation). The majority of cases of anaphylaxis are IgE-mediated, in which antibodies to a specific allergen activate mast cells and basophils, leading in degranulation and the release of a range of chemical mediators. Non-immune anaphylaxis is caused by either direct activation of mast cell and basophil receptors or

by complement activation. Clinically, it is impossible to distinguish between the two forms, and the therapy is the same for both. [4]

Although no cases have been reported in Rwanda, there are around 401 case reports recorded in the WHO global database retrieved when using "Salbutamol (Active ingredient)" as the search criteria for the drug, and "Anaphylactic reaction (PT), Anaphylactic shock (PT), Anaphylactoid reaction (PT), Anaphylactoid shock (PT)" as the search criteria for the reaction. [5] The analysis of global case reports shows a consistency and a positive temporal relationship of the concerned drug-event combination. In the global database (VigiLyze), 60.8% of the 401 cases were female, while 35.2% were male. The majority (51.6%) were experienced by individuals aged 45 years and above. [5]

Even though the described anaphylaxis/anaphylactic shock when using Salbutamol is not clinically clear and specific, as there were concomitant medications in some cases, VigiLyze data show that the performed causality assessment for 72 case reports was classified as certain and/or probable for 23 cases (certain-5 cases and probable-18 cases) and as possible for 35 cases. [5]

Although anaphylaxis/anaphylactic shock is not labelled in the SmPC of Salbutamol, the potential risk of anaphylaxis/anaphylactic shock after the administration of Salbutamol is possible because the same drug-event combination is labelled in the SmPC of Salmeterol, another drug that is Beta-2 adrenergic agonist. [6] Additionally, the National Health Services (NHS) of the United Kingdom confirmed anaphylaxis as a serious allergic reaction to Salbutamol. [7] Some of the risk factors for severe or fatal anaphylaxis include coexisting asthma, mast cell disorders, age older than 50 years, and underlying cardiovascular disease among others. [4]

3. *Information to Consumers/Patients/Caregivers*

- Patients should be aware of a potential risk of developing anaphylaxis/anaphylactic shock to Salbutamol.
- Patients should be advised to consult the Physician or Pharmacist prior administration of Salbutamol.
- If ever experienced a serious allergic reaction to Salbutamol, patients should inform a healthcare professional and seek a different treatment.

4. *Information to Healthcare Professionals*

- Healthcare professionals should be aware of the potential risk of anaphylaxis/anaphylactic shock to Salbutamol sulfate.
- Healthcare professionals should be aware that some of the risk factors for severe or fatal anaphylaxis include coexisting asthma, mast cell disorders, age older than 50 years, and underlying cardiovascular disease among others. Therefore, cautions should be taken when Salbutamol is prescribed for these patients.
- Healthcare professionals should no longer prescribe or dispense Salbutamol to patients who are at high risk of developing or who have experienced serious allergic reactions to Salbutamol including anaphylaxis/anaphylactic shock.
- Healthcare professionals are requested to gather more evidence through collection and submission of cases reports to Rwanda FDA of any encountered anaphylaxis/anaphylactic shock to Salbutamol in

order to guide the Authority on further assessment of this signal and taking appropriate regulatory action.

5. *Reporting Channel*

Patients and Healthcare Professionals are urged to report any suspected serious adverse drug reactions associated with Pholcodine-containing regimens and other medicines/vaccines to Rwanda FDA by completing ADR/AEFI reporting form accessible on Rwanda FDA website via the link https://rwandafda.gov.rw/wp-content/uploads/2022/11/ADR_AEFI_Reporting_form.pdf and the filled form should be sent to the email: pv_sm@rwandafda.gov.rw and copy to info@rwandafda.gov.rw.

Sincerely,

Prof. Emile BIENVENU
Director General

23/08/2023

6. *References*

1. Pharmaceuticals and Medical Devices Agency (2021) *Important Safety Information*. Available at: https://www.pmda.go.jp/files/000240380.pdf#page=11 (Accessed: 25 July, 2023).
2. Electronic Medicines Compendium (2023) *Easyhaler-Salbutamol*. Available at: https://www.medicines.org.uk/emc/product/6339/smpc#gref (Accessed: 26 July 2023).
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4. American Family Physician (2020) *Anaphylaxis: Recognition and Management*. Available at: https://www.aafp.org/pubs/afp/issues/2020/0915/p355.html (Accessed: 26 July, 2023).
5. WHO-UMC-VigiLyze (2023) 'Salbutamol and anaphylaxis'. Available at: https://vigilyze.who-umc.org/ (Accessed: 26 July, 2023).
6. Electronic Medicines Compendium (2023) Salmeterol. Available at: https://www.medicines.org.uk/emc/product/848/smpc/print (Accessed: 25 July 2023).
7. National Health Services (2021) *Salbutamol inhaler*. Available at: https://www.nhs.uk/medicines/salbutamol-inhaler/ (Accessed: 28 July 2023).