RWANDA FDA
Rwanda Food and Drugs Authority

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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DEAR HEALTHCARE PROFESSIONAL

Medicine	Safety information
Bupivacaine	**Cardiotoxicity following bupivacaine administration.**

1. Introduction

Reference is made to the Rwanda FDA's analysis reports of 5 adverse drug reactions reports through spontaneous reports from hospitals reporting cardiotoxicity following bupivacaine administration.

Further reference is made to the Summary of Products Characteristics (SmPC) of bupivacaine injection especially in its section 4.8 and 4.4 related to undesirable effects, special warnings and precautions for use of bupivacaine. The mentioned sections of SmPC states that bupivacaine may cause cardiac events, acute toxicity effects on the central nervous and cardiovascular systems if utilized in anaesthetic procedures resulting in high blood concentrations of the medicinal product[2].

Bupivacaine is a local anesthetic used in a wide variety of superficial and invasive procedures[3]. Bupivacaine is a long-acting local anesthetic agent that is very widely used for cutaneous infiltration, peripheral nerve blocks, epidural anesthesia, and spinal anesthesia.

Bupivacaine (BP) utilized for intraoperative local anesthesia, post-operative analgesia and in the treatment of chronic pain. BP is widely used in obstetrics. In lumbar epidural anesthesia, the drug appears innocuous to mother and fetus. Systemic toxic reactions, especially cardiac arrhythmias and cerebral convulsions, may occur during BP epidural analgesia because of fast absorption leading to high plasma peak levels.[4] The cardiotoxic effects being enhanced by hypoxia, hypercapnia, acidosis and hyperkalaemia. It inhibits cardiac conductivity and contractility, and may induce ventricular fibrillation. Bupivacaine therefore should not be used for patients with cardiac disease.[1]

2. Description of the safety information

Bupivacaine is an amide local anesthetic that provides local anesthesia through blockade of nerve impulse generation and conduction. These impulses, also known as action potentials, critically depend on membrane depolarization produced by the influx of sodium ions into the neuron through voltage-gated sodium channels3.

Bupivacaine blocks many ion channels in the heart muscle, causing severe cardiotoxicity. Small-conductance calcium-activated potassium type 2 channels (SK2 channels) are widely distributed in the heart cells and are involved in relevant physiological functions4.

Bupivacaine crosses the neuronal membrane and exerts its anesthetic action through blockade of these channels at the intracellular portion of their pore-forming transmembrane segments. The block is use-dependent, where repetitive or prolonged depolarization increases sodium channel blockade. Without sodium ions passing

through the channel's pore, bupivacaine stabilizes the membrane at rest and therefore prevents neurotransmission.

Rwanda FDA warns healthcare professionals about the closed signal of Cardiotoxicity following bupivacaine administration, Bupivacaine should be used with precautions in patients with cardiac disease, renal insufficiency, and hepatic diseases.

3. *Information to Consumers/Patients/Caregivers*

- Patients are encouraged to report any suspected adverse event associated with the use of bupivacaine to healthcare professionals or to Rwanda FDA.

4. *Information to Healthcare Professionals*

- Be aware on serious cardiac events including cardiotoxicity and cardiac arrest then prepare accordingly before administering Bupivacaine
- Limit the dose of bupivacaine to the lowest effective dose then assess the signs of LAST (local anesthetic toxicity)
- Emergency resuscitation equipment should be available whenever local region anesthesia is injected to allow quick intervention in case of serious events
- Considering the types of bupivicaine (Isobare and hyperbale) then positioning patient accordingly.

5. *Information to Marketing Authorization Holders*

- Marketing Authorization Holders are recommended to raise awareness on possible risk minimization measures for the mentioned risk of cardiac events by ensuring the clear description and awareness of the events in both Patient information leaflet (PIL) and Summary of Products Characteristics (SmPC).

6. *Reporting Channel*

Healthcare Professionals and patients are urged to report any suspected serious adverse events associated with the use of Bupivacaine and other medicines to Rwanda FDA by completing ADR/AEFI reporting form accessible on the 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

7. *References*

1. Health Products Regulatory Authority, Summary Product Characteristics accessible of Bupivacine 5mg/5ml accessible on https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0073-091-002_17102019162028.pdf

2. J J Eledjam, J E de la Coussaye, B Bassoul, J Brugada, Mechanisms of the cardiac toxicity of Bupivacaine accessible on https://pubmed.ncbi.nlm.nih.gov/3408033/#:~:text=Of%20all%20the%20amide%20local%20anaesthetics%2C%20bupivacaine%20is,either%2C%20electrical%20and%20mechanical%20structures%20within%20the%20heart.

3. Hongfei Chen, Zhousheng Jin, Fangfang Xia, Zhijian Fu, Bupivacaine inhibits a small conductance calcium-activated potassium type 2 channel in human embryonic kidney 293 cells accessible on https://bmcpharmacoltoxicol.biomedcentral.com/articles/10.1186/s40360-021-00481-2#auth-Hongfei-Chen-Aff1-Aff2

4. EMC, Bupivacaine 5mg/ml solution injection accessible on https://www.medicines.org.uk/emc/product/11612/smpc