

## Concerns on Generic Enoxaparin use in Acute Coronary Syndrome

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### Dear Editor,

Several generic low molecular weight heparins (LMWHs) have been recently used in different parts of the world. In South America, numerous generic versions of enoxaparin are available. Clinical bioequivalence data on these agents are not available<sup>1</sup>. However, some of the studies have compared these agents for their pharmacokinetic and pharmacodynamic actions. Different studies have also shown in the *in vitro* settings and experimental animals that some of these agents are different<sup>2,3</sup>. In addition to the use in deep venous thrombosis (DVT) management, these drugs are also used in acute coronary syndromes (ACS).

The role of enoxaparin in ACS is well established<sup>4,5</sup>. use Doses of 1mg/kg BID in NSTEMI patients for up to 10 days represent the highest dose that may present a greater accumulation potential than the usual one for other indications, such as DVT prophylaxis.

In STEMI patients, an initial dose of 30 mg IV followed by 1mg/kg SQ also represents a higher dose, where circulating levels can reach up to 1 U/ml in the initial stages<sup>6</sup>. As these patients are mostly treated with antiplatelet agents and other drugs, the potential drug interactions are amplified, which can result in bleeding complications.

In the case of a patient undergoing percutaneous coronary intervention (PCI), previously treated with enoxaparin, a time-window of 8 hours is stipulated for heparinization. Regardless of that, unfractionated heparin (UFH) and enoxaparin have significant drug-drug interactions, which can result in enhanced bleeding. Moreover, many of these patients are treated with thrombolytic agents and anti-platelet drugs, with variable dosing. Thus, this procedure also represents a complicated regimen, which has a low-safety margin.

The generic versions of enoxaparin have been widely used in India and South America, for ACS management without any clinical trials. Safety issues have not yet been recorded. The

initial review of the differences in the branded and generic agents clearly points to major safety concerns<sup>7</sup>.

In addition, the immunogenicity of different branded and generic products may be contributory to the safety outcome with these agents. Although patients are treated for up to 10 days, antibodies can last for up to 6 to 8 weeks and can alter the anticoagulant efficacy of these compounds. However, such data are not available. Some of the concerns related to the safety of generic enoxaparin usage in ACS are given below:

1. A full dose of 1 mg/kg BID resulting in high circulating levels may have a higher risk of bleeding due to several complicating factors.
2. Interactions with antiplatelet agents, which may vary with different drugs and drug combinations.
3. Interaction with thrombolytic agents may also vary, depending upon the type of the agent used and the timing.
4. Potential unknown interactions with newer anticoagulants such as dabigatran, rivaroxaban and apixaban.
5. Drug over-accumulation in renal-impaired patients.
6. Conversion from clinical treatment of ACS to PCI or CABG and the consequences of potential interactions between on-board enoxaparin and UFH IV, while on full dosage
7. The primary outcomes and incidence of peri-procedural complications, such as primary ischemic outcomes (MI), bleeding and catheter thrombosis have been addressed for the branded enoxaparin and UFH. These concerns, however, have not been adequately studied for the branded and generic products and may result in significant differences between these products. This requires clinical validation in adequately powered trials.
8. Therefore, at this time, the use of generic enoxaparin products in this critical indication is not recommended. Moreover, simply carrying out studies of bio-equivalence and limited VTE prophylaxis in healthy volunteer with relatively lower doses of 40 mg OD SQ are not adequate to justify the use of generic agents in such critical cardiovascular indications as ACS.

A previous study has compared the efficacy and safety of a branded enoxaparin, namely Lovenox, with a generic form of this agent<sup>8</sup>. This study only compared the two agents in DVT settings in Brazil. It called for larger studies for statistical validation. We would like to caution that the results of these studies cannot be extrapolated to other indications, particularly in ACS. Any claims by the

### Key words

Enoxaparin/adverse effects; drugs, generic; acute coronary syndrome.

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company or parties regarding the clinical equivalence of a generic product must be validated in a proper clinical trial. As authors of the unpublished trial, we wish to state that pharmacodynamic differences in doses may contribute to clinical differences and must be taken into account. We also stress that the use of generic enoxaparin in indications

such as ACS must be validated by clinical trials prior to its approval. Therefore, it is necessary for the regulatory authorities to consider this proposal. As with the branded LMWHs, each of the generic products must be compared for its efficacy and safety in different indications in well-designed and powered clinical trials.

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