European Medicines Agency
Evaluation of Medicines for Human Use

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OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE PURSUANT TO ARTICLE 5(3) OF REGULATION (EC) No 726/2004, FOR HEPARINS

Basis for opinion

On 24 April 2008, Germany submitted a request to the CHMP for an opinion under Article 5(3) of Regulation (EC) No 726/2004 on the most appropriate short, mid and long term strategies to manage the reported contamination of medicinal products containing or derived from heparin. This was triggered by numerous reports of severe, including some fatal, adverse drug reactions (ADRs), largely allergic in type and involving severe hypotensive episodes, following intravenous use during dialysis procedures reactions associated with unfractionated heparin (UFH) products in the US and Germany. In both countries, the heparin products associated with the ADRs were found to be contaminated with over-sulphated chondroitin sulphate (OSCS) and different Chinese manufacturers were identified as the source of the active pharmaceutical ingredient (API).

Subsequently, all contaminated UFH products have been withdrawn from the EU market or quarantined. The situation is different with some low molecular weight heparins (i.e. enoxaparin), where in some cases the use of contaminated product has been allowed due to limited product availability.

Specifically, the Committee has been requested to provide advice on the following four issues:

1. On the basis of available data, what is the Committee's scientific assessment on (a) the levels of risk associated with the usage of medicinal products containing or derived from heparin which may contain various levels of OSCS or other possible impurities and (b) the possible underlying biological mechanisms associated with the adverse reactions?

2. The most appropriate risk minimisation strategies and advice to healthcare professionals to continue treatment with these important life-saving medicines taking into account possible shortages of uncontaminated products.

3. Given that this is an international problem and the need to ensure the best use of scarce resources, the Committee is asked to advise on the appropriate co-ordinated approach to examine how contamination arose in the supply chain.

4. Appropriate measures to minimise the possibility of future contamination.

The official request is appended to this opinion (Appendix 1).

On the basis of the request made by Germany, the CHMP considered that there were sufficient grounds to start the procedure.

The procedure started on 25 April 2008.

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Overall conclusions

There are no implications for the product information (SPC, labelling and package leaflet) of any of the examined products.

The CHMP, having considered the matter as set out in the annexed assessment report (Annex 1), concludes the following short term recommendations and actions. The CHMP may decide to issue updated advice and/or recommendations in the context of this art 5(3) procedure in the light of new information.

On the levels of risk associated with the usage of heparin medicinal products which may contain various levels of OSCS or other possible impurities and the possible underlying biological mechanisms associated with the reported adverse reactions.

- Based on the analysis of ADR reporting, there is evidence of a causal association between the reported severe ADRs and intravenous use of UFH batches contaminated with 17 - 21% OSCS. The available data do not allow identification of a patient population who may be at increased risk of such ADRs.
- The evidence does not allow a clear dose-response relationship to be established (in terms of either dose of heparin containing OSCS and/or level of OSCS contamination), hindering the formulation of robust risk minimisation measures in relation to product with differing levels of contamination.
- The risks, if any, associated with subcutaneous administration of low level (< 7%) OSCS in enoxaparin remain uncertain, as no clear pattern of adverse reactions has been identified with these levels of OSCS and this route of administration. However, it is reassuring that despite more than 5 months marketing experience with contaminated enoxaparin in the EU, no specific risks have been identified.
- The study by Kishimoto *et al*[1] provides good evidence of a plausible biological mechanism through which OSCS may induce a severe allergic response, namely through activation of the kinin-kallikrein system, generation of C3a and C5a and activation of factor XII. However, it remains unclear whether this is the sole mechanism of action involved in the reported anaphylactoid reactions, as an allergic mechanism involving IgE, degranulation of basophils or mastocytes, independent of OSCS, or a combination of such mechanisms, cannot be excluded.
- There is insufficient evidence to assess whether the levels of dermatan sulphate identified in some products are associated with any specific risks.

There are no data on which to assess the risk of foetal exposure to OSCS-contaminated heparins.

On the most appropriate risk minimisation strategies and advice to healthcare professionals to continue treatment with these life-saving medicines taking into account possible shortages of uncontaminated products.

As there is no current shortage of uncontaminated UFH, only batches free from contamination should be released and used.

[1] N Engl J Med 2008, 358 ff

LMWH is a life saving medicine and given the lack of evidence of risk associated with subcutaneous use of enoxaparin with up to 7% OSCS contamination, Member States should make decisions on release of contaminated enoxaparin based on the need to maintain supply at national level. The following temporary advice is recommended in those Member States where use of OSCS-contaminated enoxaparin is needed in order to maintain supply:

- Health professionals should be advised to avoid intravascular administration of enoxaparin where possible.
- In all cases where contaminated enoxaparin has to be used, prescribers should be alerted to the possibility of severe allergic reactions and be prepared to administer standard therapies (e.g. vasopressor treatment and steroids).
- There is no evidence of a risk of subcutaneous enoxaparin contaminated with up to 7% OSCS to the foetus. However, on a precautionary basis, use of contaminated enoxaparin should be avoided where possible.

Prescribers should be encouraged to report any cases of severe allergic reactions and should carefully note (a) other possible factors related to the reaction (e.g. other medications) (b) the precise nature, time course and outcome of the reaction (c) any treatment that was administered and (d) exact product details including batch number.

The above recommendations are relevant as long as the availability of heparin-containing medicinal products is jeopardised.

Given that this is an international problem and the need to ensure the best use of scarce resources, the Committee is asked to advise on the appropriate coordinated approach to examine how contamination arose in the supply chain.

Following consultation with the GMP/GDP Inspectors Working Group it is proposed to take a coordinated EU approach to investigate and inspect the heparin supply chain in collaboration with international partners. This will involve a harmonised approach to the review of the heparin supply chain, including finished product manufacturers, active substance and intermediate suppliers as well as any distributors and brokers involved. A coordinated EU inspection programme will be developed taking into account previous inspections performed either by EEA competent authorities or international partners and will include collaborative inspections involving EEA and other authorities.

The Committee should also give its opinion on appropriate measures to minimise the possibility of future contamination.

- A need to strengthen legislation and supply chain supervision at local level, in this case in China, has been identified. The European Commission should consider this in its international collaboration activities.

- The Heparin monographs in the European Pharmacopoeia should be updated to include specific tests for OSCS and other possible contaminants.

- The potential for modifications to the existing legal and regulatory framework to strengthen supply chain control should be also explored with the European Commission.

The scientific background leading to the above recommendations is set out in Annex I.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

This opinion is forwarded to Germany, all other Member States, Iceland and Norway, together with its annex and appendices.

The opinion is published on the EMEA website with its annex and appendix.

London, 30 May 2008

On behalf of the CHMP
Dr Eric Abadie, Chairman