European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 30 May 2008
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CHMP ASSESSMENT REPORT

FOR

MEDICINAL PRODUCTS CONTAINING OR DERIVED FROM HEPARIN

under Article 5(3) of Regulation (EC) No 726/2004

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BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Article 5(3) of Regulation (EC) No 726/2004

On 24 April 2008, Germany presented to the CHMP a request for an opinion under Article 5(3) of Regulation (EC) No 726/2004 following detection of a contaminant in a limited number of batches in some Member States of the European Union in the context of their overall benefit/risk profile. This was due to concerns on the impact of the benefit-risk balance of these products.

1.2 Steps taken for the procedure

- During the April 2008 CHMP meeting the following was agreed:
- Dr. Enzmann, German CHMP Member, was appointed Rapporteur for the review procedure under Article 5 (3) for the heparin containing products.
- Dr. Suvarna, UK CHMP alternate Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for the heparin containing products.
- Dr. Lechat, French CHMP alternate Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for the heparin containing products.
- A 30 day-time frame for the procedure was set.
- The procedure started on 24 April 2008.
- The Rapporteur's Assessment Reports on Questions 1 and 2 were circulated to all CHMP members on 14 May 2008 (see Appendix 1).
- The GMP/GPD inspectors working group were consulted on Questions 3 and 4 on 1 May 2008 and adopted possible approaches on their plenary meeting on 20-22 May 2008.
- On 30 May 2008, the CHMP adopted an opinion concluding that no public health concerns have been identified that are considered as being of Community interest which would warrant an Article 31 referral.

2 SCIENTIFIC DISCUSSION

Background

On the 6 of March 2008 the European Medicines Agency (EMEA) was made aware of a Rapid Notification Class I for one specific Heparin Sodium batch manufactured by RotexMedica GmbH Arzneimittlewerk which was distributed in Germany. As a consequence, The German authorities recalled this batch and a number of related batches of Heparin Sodium as a precautionary measure.

The EMEA and national competent authorities (NCA) were aware of reports in the USA relating to heparin products primarily manufactured by Baxter (using active pharmaceutical ingredient (API) manufactured in China), and suggested links to a large number of adverse events. The adverse events included profound and refractory hypotension, and serious allergic reactions, including some deaths. However the relationship of the adverse events to the heparin or to oversulphated chondroitin sulphate (OSCS) remained unclear (“causality not definitely established”).

Subsequent information received from the FDA indicated that the ADRs may be due to the presence of a contaminant, which has now been identified as OSCS. No similar adverse events have been observed after administration of low molecular weight heparins (LMWH).

On 24 April 2008, Germany requested to the CHMP, in accordance with Article 5(3) of Regulation (EC) No 726/2004, to draw up an opinion following detection of a contaminant in a limited number of batches in some Member States of the European Union. The Committee was asked to give its scientific opinion on the most appropriate short, mid and long term strategies to manage the reported contamination of medicinal products containing or derived from heparin. This included assessment on risks associated with contaminated heparin, the biological mechanisms associated with adverse

reactions, risk minimisation strategies taking into account possible shortages of uncontaminated products. The CHMP were also asked for advice on the appropriate co-ordinated approach to examine how contamination arose in the supply chain and appropriate measures to minimise the possibility of future contamination.

2.1 Article 5(3) of Regulation (EC) No 726/2004

The Committee was asked to give its scientific opinion on the most appropriate short, mid and long term strategies to manage the reported contamination of medicinal products containing or derived from heparin. The issues covered by the referral are stated below:

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 Committee is asked to give its opinion on the most appropriate risk minimization 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 advice on the appropriate co-ordinated approach to examine how contamination arose in the supply chain.

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

2.2 CHMP assessment of contamination oversulphated chondroitin sulphate in medicinal products containing or derived from heparin

Question 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?

Analysis of suspected ADR data

- Unfractionated heparins (UFH)

The EMEA approached 7 MAHs of sodium heparin products for information to address the questions above. The main source of data underpinning the analysis of ADR reports are from the US and Germany. There are too few case reports with sufficient clinical information from other countries to support an assessment.

On the basis of the available ADR case reports received, it is not possible to use these data to draw firm conclusions on the level of risk associated with OSCS-contaminated UFH. The available data also do not allow an assessment of dose-relationship (either dose of contaminated heparin or level of OSCS contamination in particular batches) nor do they support formulation of robust risk minimisation measures.

The observed ADRs were most likely due to a severe hypersensitivity reaction leading to a shock-like episode similar to anaphylaxis. In many cases, the episode was successfully treated with a vasopressor, oxygen therapy and steroids. Anaphylaxis is a recognised side effect of treatment with UFH. It is

therefore not possible to distinguish between such events due to this intrinsic risk of heparins or those due to OSCS contamination. Also, the available information on individual cases is too sparse to assess any differences in the manifestation of such events due to contaminated product compared to those due to 'normal' heparin.

The time-trend in reporting of such ADRs in the context of when contaminated product was marketed in the US and Germany provides the most useful information in assessing causality. On the basis of the sharp increase in reporting of such events after contaminated product was marketed, there is little doubt that OSCS contamination of the products was causally associated with this observed increase in reporting. It may be argued that increased public awareness of the issue may have contributed to an increase in reporting of allergic events regardless of any OSCS contamination. However, as this increase in the US was observed before widespread publicity of the issue, and as such reporting has decreased following product recall, this is unlikely to have significantly contributed to the observed increase.

The study by Kishimoto *et al* (N Engl J Med 2008, 358 ff) provides further strong support for a causal association with OSCS contamination. This study found a plausible biological mechanism for the severe allergic events observed; there is a correlation between the exposure to the OSCS contaminant and the activation of the complement cascade triggered by the kinin-kallikrein-bradykinin system of the contact phase of the coagulation system. The increased generation of the known blood pressure lowering anaphylatoxins C3a and C5a was induced in animal experiments. The study also suggests that, at least at levels of OSCS contamination > 5%, there is no dose-response effect (i.e. the effect may be all or nothing). These levels in the assays may correlate with plasma concentrations associated with the events in the US and Germany.

The vast majority of events reported were in association with an IV bolus administration during haemodialysis procedures. Whether this is simply a reflection of relative usage or the fact that a patient's first treatment is usually an IV bolus, or whether it suggests that such a route of administration and indication carries a greater risk, is unclear. However, without a clear dose-response relationship, there is no reason to suspect that intravascular exposure for other procedures would carry less risk.

It remains unclear how many of the fatal cases reported in the US were causally associated with the reported allergic reaction. It is also unclear the reason why none of the cases reported in Germany were associated with a fatal outcome. This could be due to a variety of factors such as patient characteristics including (e.g. indication, background morbidity) or local practice in identifying/managing anaphylaxis. It could also be due to a dose-response effect (i.e. the US product had 21% contamination vs 17% in Germany). However, bearing in mind the findings of Kishimoto *et al*, any such conclusion would be purely speculative based on currently available information. Furthermore, based on the findings of Kishimoto et al, if there is a lack of a dose-response effect (at least at OSCS levels above 17%), it may not be possible to implement risk minimisation measures such as dose reduction, slow infusion etc. Given that the vast majority of use of UFH is via the IV route, it is therefore appropriate that contaminated be withdrawn from use entirely.

- Low molecular weight heparins (LMWH)

The EMEA approached 5 MAHs of LMWH products. Based on responses provided by MAHs and NCAs, the only LMWH so far known to be contaminated with OSCS and marketed is enoxaparin. Therefore, only data associated with enoxaparin have been assessed.

It is not possible to draw firm conclusions on the level of risk associated with OSCS-contaminated LMWHs or formulate robust risk minimisation measures due to the fact that there are very little data available from individual ADR case reports. It remains unclear what, if any, risks may be associated with low level (up to 7%) OSCS contamination of enoxaparin given subcutaneously, or indeed how any risks may manifest clinically. Therefore, the most feasible approach in assessing such risks is to take a broad overview of ADR reporting trends, relative to market exposure, to identify any possible change in frequency or nature of reporting.

The MAH has stated that the first batches of OSCS-contaminated enoxaparin were supplied in the EU on 13 August 2007. However, the bulk of such supply began in January 2008. At present, there is currently no clear evidence of any change in frequency or nature of ADR reporting in association with enoxaparin across the EU. The slight increase in ADR reporting in the US is likely an artefact of publicity given that contaminated product has not been supplied in the US.

A critical limitation of this analysis is the reliance on passive ADR reporting and the fact that there is often a delay in ADR reporting relative to the ADR onset date. However, it is somewhat reassuring that no clear change in reporting has been observed despite affected product being marketed since January 2008. Nonetheless, it is essential that each MS continues to actively monitor ADR reporting in association with enoxaparin. It is possible that the recent recalls and public awareness of the issue in some MSs will stimulate ADR reporting and, therefore, this must be taken account when assessing passive ADR data.

It is currently unclear whether sc administration of enoxaparin, regardless of level of OSCS contamination, may carry a risk of severe allergic reactions similar to that seen with contaminated IV unfractionated heparin. The study by Kishimoto *et al* did not specifically explore such a risk. Based on the Kishimoto *et al* assays, there may be a dose-response relationship with lower levels of OSCS contamination (up to 5%), but the clinical relevance of this is unclear. The MAH for enoxaparin is currently assessing the risk of subcutaneous administration in an animal model.

Enoxaparin may also be administered via the IV (off-label) or arterial-line routes. If OSCS contamination up to 7% does indeed carry a risk of severe allergic reactions, cases may occur during such usage. There are currently no case reports of such ADRs. Given that many MSs have taken the precautionary measure of advising prescribers against such use until supply chains are free of contaminated product, it may be that no ADRs associated with such use will now be reported. The actual level of IV use is currently unclear.

On the basis of the adverse events observed with contaminated UFH and the findings of Kishimoto *et a*l, it is plausible that IV or arterial administration of enoxaparin with up to 7% OSCS contamination could induce similar allergic ADRs. The precautionary risk minimisation measure of advising prescribers not to administer [affected] enoxaparin via the IV or arterial route, until the supply chain is free of contamination, is entirely appropriate and justified.

Withdrawal of all contaminated enoxaparin would lead to severe supply shortages across the EU putting patient's lives at risk. Given the lack of evidence of any change in ADR reporting patterns in the 4 months since contaminated enoxaparin has been supplied in the EU, the approach of allowing release of enoxaparin on a batch and country-specific basis, for subcutaneous use, is also justified in order to ensure continuity of supply.

There are insufficient data to draw any conclusions on a potential risk of contaminated LMWH to the foetus. The chemical structure of OSCS and its large molecular weight suggest that the crossing of the placenta barrier is limited and similar to that of heparins. However, taking into account the results published by Kishimoto *et al*. the MAH has been asked to further investigate possible adverse effects on the foetus of C3a and C5a in the maternal circulation.

Question 2

The Committee was also asked to give its opinion on 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.

To gather information on this question a Non-Urgent Information (NUI) was sent on 30 April 2008 to the Member States to obtain an overview of the regulatory measures already taken by EU authorities and the regulatory measures they are planning in case of a shortage of uncontaminated heparin. In parallel, the EMEA sent a request to the major MAHs of heparin-containing products to receive

information about their view concerning the stock situation of their products to assess the question of possible measures during a shortage of heparin.

Planned or implemented regulatory measures concerning contaminated heparin, including actions to ensure the availability of heparin-containing medicinal products (e.g. toleration of packages with labelling in foreign language, toleration of minor amounts of OSCS).

Medicinal products containing fractionated and non-fractionated heparin in most Member States are produced with API tested with the nuclear magnetic resonance (NMR) or with the NMR and capillary electrophoresis (CE) analytical method, either voluntarily or at the request of the authorities. Some Member States have tolerated and/or continue to tolerate a low content of contamination with OSCS ($\leq$ 5%) for some medicinal products. Many Member States have no reports or have not experienced an increase in the number of ADR reports for heparin. In addition, a recall of all contaminated batches would have led to problems of availability in some Member States. Most Member States require confirmation of absence of contamination with OSCS (i.e. < the detection limit of 1% OSCS) for newly released heparin batches.

In most Member States the subject of contaminated heparin-containing medicinal products and the allergic/anaphylactic shock reactions has been communicated to the public by the relevant authorities, either via the homepage, and/or press releases, news letter and/or direct health care professional communications. In some Member States warnings were issued to avoid the usage of minor contaminated products for intravenous use.

In summary, the responses from the Member States suggest that the stock situation for UFH is not critical. The stock situation for medicinal products containing fractionated heparin seems to be different. In a number of Member States it was necessary to tolerate products with minor contamination with OSCS to assure the availability of these products. A close monitoring of the stock situation is still necessary.

How many batches of heparin-containing medicinal products were recalled or embargoed in your country? What were the batch numbers and the affected MAHs?

The relevant information has been provided by Member States. In many Member States batches of heparin-containing medicinal products were recalled voluntarily by the MAH. In some Member States batches of heparin-containing medicinal products were embargoed. These batches could be re-evaluated batch per batch if necessary to avoid a shortage on the market.

Availability of heparin-containing medicinal products according to MAHs

The relevant information has been provided and the situation varies across products. It seems difficult to determine the future stock situation given the possible measures the different Member States might apply.

Assessment of contamination oversulphated chondroitin sulphate (OSCS)

This is discussed under question 1.

Dermatan sulfate

The relationship of increased generation of the anaphylatoxins C3a and C5a after activation of the kallikrein-system as observed for OSCS-contaminated heparin has so far not been observed after application of dermatan sulphate. The currently available data seem to show no risk for this pathomechanism that would warrant a change in rating of dermatan sulphate. However, there is only little, very general information in the mentioned publication making a definitive evaluation difficult.

Recommendation

LMWH is a life saving medicine and given the lack of evidenced 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.

Question 3

Given that this is an international problem and the need to ensure the best use of scarce resources, the Committee is asked to advice 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.

Question 4

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.

3 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Following review by CHMP, a number of recommendations and actions have been proposed.

Recommendations

Short term CHMP recommendations are reflected in the published CHMP opinion.

Actions

The following actions will be carried out during the coming months. In the light of new information, the CHMP may decide to issue updated advice and/or recommendations in the context of this art 5(3) procedure.

- To collect and assess new ADR reports and information on the mechanisms causing anaphylactic reactions.

- To collect and assess results from ongoing quality tests on a regular basis (raw material and finished products).

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

- To gather precise information on the supply of heparin from various sources, mainly China. The Rapporteurs will inform CHMP on a quarterly basis.

- To review 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 MAH for enoxaparin should provide an update to the CHMP outlining the supply situation at a frequency to be decided by the CHMP.

4. ANNEXES

1. Rapporteur's Assessment Report
2. Co-Rapporteur's Assessment Report

Annex 1

Rapporteur’s Assessment Report

Annex 2

Co-Rapporteur’s Assessment Report