



QUESTIONS AND ANSWERS ON HEPARINS

The European Medicines Agency (EMA) has reviewed the issues related to the contamination of medicines containing or derived from heparins. Because of shortages, the EMA's Committee for Medicinal Products for Human Use (CHMP) is of the opinion that batches of medicines containing enoxaparin (a type of heparin), which are known to contain low levels of 'oversulphated chondroitin sulphate' (OSCS, a contaminant), can continue to be used, provided that measures are put in place to reduce the risk that may be associated with the use of such products.

What are heparins?

Heparins are anticoagulant substances (blood thinners, used to prevent and treat blood clots). They are used widely in patients for whom it is essential to keep the blood flowing freely, such as patients who could have, or have had a heart attack, in patients who have undergone major surgery, or patients on dialysis (a blood clearing technique).

Heparins are classified according to their 'molecular weight'. Molecular weight refers to the size of the molecule of heparin. Heparin in its natural state is a long chain of sub-units. Standard heparins with the longer chains are known as unfractionated heparins, while heparins with fewer sub-units are referred to as 'low molecular weight heparins' (LMWHs). Standard heparins are normally given by intravenous injection or infusion (direct injection into a vein or drip into a vein), and their effect on clotting needs to be closely monitored after administration. LMWHs can be given subcutaneously (injection under the skin) and do not require such close monitoring. This means that they can be used by patients outside hospitals.

What is happening with heparins?

In March 2008, the EMA was made aware by the U.S. Food and Drug Administration (FDA) of a problem of contamination of heparin products with OSCS. The contamination had been traced to heparin made in China.

Patients receiving heparin containing high levels of OSCS can experience severe side effects, such as extremely low blood pressure and serious allergic reactions. These side effects have been seen in patients who were given standard heparins and most often when these were given as an intravenous injection. While in the U.S. some patients have died, no such fatal events have been reported in Europe.

As a consequence, regulatory authorities worldwide have identified and recalled medicines containing OSCS. When there is a recall, all batches of a medicine must be removed from the market and returned to the manufacturer. During a recall, it is important to ensure that alternative medicines are available so that patients can continue to be treated.

OSCS has been identified mainly in medicines containing standard heparins, but it has also been found in low levels in enoxaparin, a LMWH. As there is an adequate supply of standard heparins on the EU markets, a full recall of affected batches has already taken place in the European countries where they had been distributed. But because of shortages, it is not possible to recall all of the medicines containing enoxaparin. Therefore, it is important to see if the contaminated enoxaparin batches can be used for a limited period of time until new supplies of non-contaminated material becomes available.

Why did the EMA review heparins?

The German national medicines agency, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), requested that the CHMP gives its scientific opinion on the most appropriate short-, mid-

and long-term strategies to manage the use of products containing or derived from heparin which may contain various levels of OSCS. The BfArM requested the review under an ‘Article 5(3) procedure’. This procedure is described in Article 5(3) of Regulation (EC) No 726/2004 and results in a CHMP scientific opinion, which will be made publicly accessible.

What is the opinion of the CHMP?

The CHMP acknowledged that there is a link between high levels of OSCS in heparin and the severe side effects seen in patients. However, the Committee also noted that these side effects have not been observed with any LMWHs.

As a short-term strategy, the CHMP was of the opinion that LMWHs, particularly enoxaparin, that contain low levels of OSCS (less than 5%) can continue to be used until they are replaced by OSCS-free batches provided that measures are put in place to minimise the risk of side effects. The measures include avoiding using the intravenous or intra-arterial routes, and making sure that patients treated with contaminated batches are closely monitored for allergic reactions. As a precautionary measure, the CHMP also recommended that doctors should also avoid using these products in pregnant women.

For any mid- to long-term strategy, the CHMP was of the opinion that it is necessary to operate in a coordinated way within the EU to address all issues relating to the contamination. This includes any investigation into the origin of the contamination and any inspection of factories where heparins are made. In addition the CHMP was of the opinion that an international dialogue should be started with China to strengthen supervision of manufacture.

The CHMP also recommended that the European Pharmacopoeia monograph for heparins (the standard that describes how to check the quality of heparins) be updated to include the tests for detecting OSCS.

What are the consequences for patients and doctors?

- Patients should continue using the heparin they have been prescribed as instructed by their doctor. Patients should contact their doctor if they have any concerns.
- Doctors who prescribe enoxaparin must be aware of the current contamination issue. Country-specific advice on heparins and information on stocks and potential shortages are available in all affected Member States. OSCS-free enoxaparin is becoming available and is gradually replacing contaminated enoxaparin in the supply chain.
- When giving OSCS-contaminated enoxaparin, doctors should:
 - avoid giving enoxaparin directly into an artery or vein;
 - closely monitor their patient for signs of allergic reactions;
 - be ready to administer the standard anti-allergy treatments, should such a reaction occur.
- Any allergic reaction should be reported, including the batch number of the medicine used.
- While there are still stocks of contaminated enoxaparin in use, doctors should avoid using the medicine in pregnant women.

What will happen next?

The CHMP opinion will be communicated to the member states, so that they act accordingly. The EMEA will update this document if new information becomes available.